

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

IN RE: '318 PATENT INFRINGEMENT)	REDACTED
LITIGATION)	PUBLIC VERSION
)	Civil Action No. 05-356-SLR
)	(consolidated)
)	

PLAINTIFFS' POST-TRIAL ANSWERING BRIEF

**APPENDIX I:
TRIAL TRANSCRIPT EXCERPTS**

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69		United States Patent and Trademark Office Memorandum, "Supreme Court decision on <i>KSR Int'l Co., v. Teleflex, Inc.</i> ", May 3, 2007

EXHIBIT 1

1

2 Q. And can you describe to the Court just generally the
3 nature of the disease from the patient's perspective?

4 A. This disease almost always begins with insidious onset
5 of the memory problems, which progress over time to develop
6 into more serious memory problems, and then begin to affect
7 other higher brain functions, such as judgment and
8 reasoning, such as language ability, such as perception and
9 recognition. It also -- so those are the cognitive aspects
10 of the disease.

11 But we've known forever that the disease also
12 affects behavioral problems. Alzheimer's first patient
13 was a woman who had paranoid delusions. It's part of the
14 illness. Personality changes are also frequently a part
15 of the illness, as is depression.

16 So it's a devastating disease that affects,
17 over the course on average of about eight to ten years,
18 individuals' cognitive abilities, their behavior and their
19 functional abilities.

20 Q. Okay. And is there a variance in the progression of
21 the disease?

22 A. There is. Just like there's variance in all of our
23 own abilities to start with, this is a disease that affects
24 everybody a little bit differently. The course of the
25 disease is very broad. Again, as I said, it's on average

1 results in enhancement of cholinergic functioning.

2 Q. Okay. What is the effect of Razadyne on a patient
3 who receives it?

4 A. The effect on a patient is that it actually varies.
5 Some patients, first of all, respond. Some people, you
6 know, don't see much of a response.

7 If you give the drug to a lot of patients,
8 overall, you'll see that there's some stabilization of
9 clinical symptoms for the most part. One might see that --
10 again, a few patients may show some benefits in memory,
11 in thinking abilities, but for the most part, there seems
12 to be some stabilization of the symptoms over about a six
13 to 12-month period, sort of in one -- what one thinks would
14 happen if the person hadn't been taking the drug.

15 Q. Is Razadyne the only cholinesterase inhibitor available
16 on the market today?

17 A. No, it's not. Also available are Exelon (phonetic)
18 and Aricept.

19 Q. And are any of those preferred at this point?

20 A. My reference is Aricept and I think that's still the
21 most widely prescribed drug. I guess I should add that I
22 guess tacrine is still theoretically available, though
23 it's not prescribed any more.

24 Q. All right.

25 A. It was FDA approved.

1 Q. The retrieval categories basically confirm the same
2 thing; is that right?
3 A. That's right.
4 Q. Now, Dr. Drachman's finding about the importance of
5 acetylcholine in memory function, was that confirmed over the
6 years?
7 A. Yes, it was. People went -- there were hundreds of
8 studies in humans and animals and in some cases they continue
9 to this day.
10 Q. Is the finding accepted to this day?
11 A. Yes, it is.
12 Q. Let's talk about Alzheimer's disease.
13 What was the next step in this progression of
14 determining the importance of acetylcholine in Alzheimer's
15 disease?
16 A. As I mentioned, there really hadn't been much work on
17 Alzheimer's disease at all until about the seventies when it
18 was believed that there was insight to senility. That led
19 people to begin to investigate for the first time in a
20 serious way the possible causes of Alzheimer's disease.
21 Really one of the first steps that led to
22 insights beyond what was already known in that plaques and
23 tangles was a discovery that there is an acetylcholine
24 deficiency associated with the actual brain disease.
25 Q. Let's go to the timeline again.

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1 What have you indicated there on the timeline?
2 - - -
3 A. One of the first groups was actually Peter Davies.
4 They reported a paper in 1976 in the Lancet.
5 Q. That should be in your folder. Defendants' Exhibit
6 139.
7 A. Yes. I have it.
8 Q. And can you just identify that by title and author
9 and publication for the record, please?
10 A. This was the title of the article was, it's a letter
11 to the editor in Lancet published Christmas Day 1976
12 entitled, selective loss of central cholinergic neurons
13 in Alzheimer's disease.
14 Q. Was this worked you relied upon in forming your
15 opinions in this case?
16 A. Yes.
17 Q. Is it a reliable authority?
18 A. Yes.
19 Q. One of the articles relevant to the level of skill
20 in the art relevant to the patent in this case?
21 A. Yes.
22 MR. LOMBARDI: I offer it, your Honor.
23 MR. SIPES: No objection.
24 THE COURT: Thank you.
25 DEPUTY CLERK: So marked.

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1 A. Well, this was one of the first times I think that
 2 the cholinergic hypothesis term was used. And it referred
 3 to the idea that a reduction in acetylcholine or the
 4 deficiency in the cholinergic containing cells contributes
 5 to Alzheimer's disease and the fact that she said
 6 functional abnormalities means that it contributes to the
 7 functional loss in Alzheimer's disease. I.e., it
 8 contributes to cognitive impairment, perhaps behavioral
 9 impairment. Just generally it contributes to actual
 10 clinical symptoms of the disease.
 11 Q. Acetylcholine contributes to the clinical symptoms of
 12 the disease?
 13 A. That's right.
 14 Q. All right. Now, with the cholinergic hypothesis
 15 out there, did that lead scientists to think about
 16 possible treatments?
 17 A. It absolutely did. That was certainly one of the
 18 most compelling aspects of this hypothesis in that the
 19 corollary of it was that it should lead one to treatment
 20 strategies.
 21 Q. And what's the fundamental -- we'll talk about
 22 various strategies, but what's the fundamental idea
 23 behind treatment strategies based on the cholinergic
 24 hypothesis?
 25 A. The cholinergic hypothesis states that basically

1 So we saw that choline is the substrate that gets turned
 2 into acetylcholine. You can actually give humans choline
 3 like through Lecithin will be --
 4 Q. Lecithin is a drug?
 5 A. Right. Or a nutritional supplement. Some might
 6 orally give supplements with the hope that it would raise
 7 acetylcholine in the brain.
 8 Q. All right. And next, please.
 9 The post-synaptic. What would be a
 10 post-synaptic treatment strategy to try to increase
 11 acetylcholine?
 12 A. It's would be to develop drugs had a that would
 13 directly stimulate the post-synaptic -- by binding to
 14 muscarinic receptors or nicotinic receptors. A direct
 15 acting agonist.
 16 Q. What's an agonist?
 17 A. A drug that mimics acetylcholine, will stimulate the
 18 receptor.
 19 Q. As of 1986, had there been any successes with the
 20 pre-synaptic approach?
 21 A. By and large results were no. Because it was such
 22 an immediately available thing to try, there had been
 23 some animal studies suggesting, there were probably 15 or
 24 so studies that were performed by the early 1980s,
 25 mid-1980s, and almost universally, the studies in humans

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1 cholinergic function is inadequate or failing and so that
 2 the premise is that when one wants to improve or restore
 3 cholinergic functioning through whatever strategy possible.
 4 Q. Just so we have this out there, is the cholinergic
 5 hypothesis sometimes also referred to as the cholinergic
 6 deficit hypothesis?
 7 A. Yes.
 8 Q. Same thing?
 9 A. Same thing.
 10 Q. Let's put the next slide up.
 11 Again, this is our slide of the synaptic region
 12 of the brain, and let's go to the next one, please.
 13 The pre-synaptic region. Were there treatment
 14 strategies considered relating to acetylcholine in the
 15 pre-synaptic region?
 16 A. There were. In fact, they were the first most
 17 immediately available ways to try to enhance the
 18 cholinergic synaptic functioning was through means that
 19 might, that were postulated to be able to increase
 20 acetylcholine synthesis and release.
 21 Q. All right. And so when we talk about pre-synaptic
 22 treatment involving acetylcholine, what -- what are you
 23 talking about doing?
 24 A. What you are really talking about doing for the most
 25 part is giving humans oral precursors to acetylcholine.

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1
2 Q. Okay. And when you say -- when it says partially
3 reverse the memory deficit, what does that indicate to you?
4 A. Well, it was clear from the get-go, you could measure
5 some improvement in memory and sometimes other cognitive
6 tests. They realized patients were not back to normal.
7 These are people with Alzheimer's disease.
8 Q. Similar to the way galanthamine works today?
9 A. Yes. Extremely difficult to see major clinical
10 benefits in most people.
11 Q. Is there a place in the article that gives a good
12 example of the results that they received in this testing?
13 A. Yes.
14 Q. And I will refer you to Page 1422.
15 A. So there on Page 1422 in the right column is Table
16 2, which I think nicely illustrates the type of results
17 that they saw and describe clear clearly in their paper.
18 Q. Okay. Well, let's start. It talks about this being
19 mean percent correct on the recognition memory test.
20 What was the recognition memory test?
21 A. The recognition memory test consisted of giving a
22 series of words, for example, or a series of pictures and
23 then asking the patient over and over to learn this long
24 list of words or pictures. Then they would come back after
25 time and show the patient the same words or the same

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1 pictures mixed with words or pictures they hadn't seen
2 before and ask, test the memory of the patient by seeing
3 if they could sort out which ones they had seen from which
4 ones they hadn't seen.
5 Q. There are ten pages. If you could describe what the
6 results are in the table, please...
7 A. Sure. Well, first of all, this was what was
8 considered the replication phase of the study, so I should
9 mention that there were two parts to the study.
10 The first part of the study, they actually
11 tested different doses in each patient as we saw in the
12 abstract, because they wanted to find the dose that was
13 best for any one patient. That turned out to be a very
14 important step in their approach to studying these drugs.
15 In the replication phase, tested that single
16 best dose that worked for any one patient and compared it
17 with placebo in a double-blinded controlled manner.
18 Q. And what column here is the column that shows you
19 the result really?
20 A. Well, the difference is shown between the placebo
21 and on the drug physostigmine is shown by the final
22 column on the right, so the chain.
23 So you can see among these ten patients who
24 had all responded in the first phase, when they were
25 given this replication phase, eight of the ten patients

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1 was used?

2 A. That's right. It's just another variation of similar
3 memory task to what we've seen before.

4 Q. Okay. And what does the table reflect about the
5 results?

6 A. What it shows is the actual percent change in how
7 much better the memory was or how much worse their memory
8 would be if that were the case on the drug versus placebo.

9 So, for example, if you look at patient one
10 there, in the first column it says sum of recall. It
11 shows there was a 19-percent improvement in their memory
12 after taking the oral physostigmine. And so what you can
13 see is you just quickly look down that column, every single
14 one of the eight, at least respond errs they showed there,
15 showed that they improved, a positive memory effect with the
16 oral physostigmine.

17 Same way when you look at another memory task,
18 this is the retrieval for long-term storage of memory, one
19 found again that there were positive -- positive responses
20 on memory that could be measured. So, again, patient one,
21 for example, showed 57-percent improvement in their memory.
22 The number of items they actually recalled was 57-percent
23 higher on the physostigmine compared to the placebo.

24 And then the third column ask is a different
25 type of memory. It's called intrusions or almost like a

1 name of which is Tetrahydro aminoacridine. So THA is
 2 tacrine.
 3 Q. Okay. And it identifies THA or tacrine as a centrally
 4 acting anti-cholinesterase; is that right?
 5 A. Yes.
 6 Q. What does that mean?
 7 A. It means it has the ability to get into the brain so
 8 it can affect higher brain functions.
 9 Q. Okay. And that's physostigmine was a centrally acting
 10 anti-cholinesterase?
 11 A. Yes.
 12 Q. Galanthamine?
 13 A. Galanthamine is a centrally acting anti-cholinesterase
 14 as well. I say cholinesterase inhibitor.
 15 Q. When we say those, when they refer to
 16 anti-cholinesterase, what does that mean with respect to
 17 cholinesterase inhibitor?
 18 A. It is a cholinesterase inhibitor.
 19 Q. Same thing. Are they used synonymously?
 20 A. Yes.
 21 Q. All right. So what is reflected in this work by
 22 summers and colleagues?
 23 A. Well, what they did is they tried giving patients
 24 with Alzheimer's disease a -- 12 unselected cases,
 25 intravenous tacrine. And then they used some memory

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1 tests and some global sort of staging tests to determine
 2 if there is a benefit on memory and what they considered
 3 as sort of a global functioning of the patients.
 4 Q. Okay. And what did they find?
 5 A. Well, what they found, as it says here, significant
 6 improvement in memory testing occurred in six of twelve
 7 subjects and nine of twelve improved in clinical staging.
 8 Q. Okay. And are those results reported elsewhere in
 9 the article?
 10 A. Yes.
 11 Q. Okay. Let's go to the next slide and Page 150.
 12 A. So on Page 150 on the top is their Table 2, which is
 13 entitled, Maximum Change in Clinical Staging after THA.
 14 Q. Okay. And let me just ask you, when it says clinical
 15 staging, what exactly is it referring to?
 16 A. Well, as I mentioned, they did a very global clinical
 17 staging, so they had sort of the health care professionals
 18 there, nurses and doctors, sort of evaluate these patients
 19 and they used this rating scale that they come up with or
 20 had been around, staging the patient zero through six.
 21 Basically, stage zero means there's no signs of dementia
 22 present when they examined the patient. Stage six would
 23 be somebody who's bed-bound and completely unresponsive.
 24 So zero is basically no clinically evident
 25 disease. Six is the most significant disease you could

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1 and to determine if the addition of an acetylcholine
2 precursor can produce greater improvement in memory than
3 physostigmine alone.
4 Q. Let's stop there. There's a reference to precursor.
5 What does that refer to?
6 A. Again, the pre-synaptic approach.
7 Q. Okay. And had there been success in the pre-synaptic
8 approach by this time?
9 A. No, there hadn't, but there were questions at the
10 time about whether combining the two might actually be more
11 effective.
12 Q. All right. And the next sentence, please.
13 A. Presently, physostigmine has limited usefulness
14 due to its very short duration of action, less than one
15 hour, and the high incidence of peripheral cholinergic
16 side effects.
17 Q. Do you have an understanding of what peripheral
18 cholinergic side effects refers to?
19 A. It means the side effects of too much acetylcholine
20 action outside the brain. For example, in the stomach,
21 the nausea and vomiting, effects on the gastrointestinal
22 system. That would be an example of peripheral side
23 effect.
24 Q. Okay. And in the last line, it says, However, it
25 has served as a useful pharmacological model.

1 that article out, please?

2 A. I have that here.

3 Q. Okay. And can you read the title of the article

4 and the authors so we have that in the record, please?

5 A. This is entitled Reversal of Central Anticholinergic

6 Syndrome by Galanthamine. It's published in JAMA, which is

7 the Journal of the American Medical Association, in 1977.

8 Q. And JAMA is an authoritative journal?

9 A. Yes. A very prestigious medical journal.

10 Q. Is this an article that you have relied upon in

11 coming to your opinions in this case?

12 A. Yes.

13 Q. Is it a reliable authority?

14 A. Yes.

15 Q. Is it relevant to determining the level of ordinary

16 skill in the art for purposes of this case in 1986?

17 A. Yes, it is.

18 Q. Okay. Let's put the article up on the screen, please.

19 And this is from the abstract. Could you first

20 describe generally the work that's described in the article,

21 please?

22 A. Okay. Well, there's a medical problem that occurs,

23 not uncommonly, where people get intoxicated or overdosed

24 with drugs that block acetylcholine. Drugs have that

25 certain property and taken too much, can cause toxicity.

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1 It's associated with confusion, delirium, hallucinations,

2 all sorts of things. And this article is about testing

3 whether galanthamine is able to reverse it or correct the

4 problem.

5 Q. Okay. And so in this case we're talking about ten

6 volunteers were given scopolamine intravenously; is that

7 right?

8 A. That's right.

9 Q. Again, this is the same scopolamine we saw referred

10 to when we were talking about studies about memory and

11 acetylcholine; is that right?

12 A. That's right.

13 Q. Okay. And so what happened when these ten

14 volunteers were given scopolamine and then galanthamine?

15 A. What they did is they obviously gave the scopolamine

16 by design rather than intoxication, which sometimes happens

17 clinically, and they gave them medicine so that -- they

18 were actually medical students. They became sleepy,

19 actually hallucinated, things like that.

20 So they developed anticholinergic syndrome.

21 They demonstrated they could do that.

22 Measured their brain waves while that was

23 occurring. And then they gave galanthamine, to see if

24 they could make the students better.

25 Q. Okay. And what happened?

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1 A. This gloomy picture is thoroughly wiped out and a
2 favorable result readily obtained when one of the
3 treatable underlying causes is detected.

4 So this is the category of dementias that he's
5 calling reversible dementias that we still consider
6 reversible dementias today.

7 Q. Okay. I'm just being obvious about that, but what's
8 a reversible dementia?

9 A. He gives the good example that we still search for
10 in every patient today, including B12 deficiency or thyroid
11 hormone deficiency. So if that's causing the dementia, one
12 could find the cause of it, it's possible you could reverse
13 the symptoms by replacing the hormone.

14 Q. Is another category of dementia referenced in the
15 second paragraph?

16 A. Yes. The second paragraph discusses the category of
17 dementia that he says can be arrested.

18 Q. What is arrested dementia?

19 A. That's when the cause of the dementia can be
20 identified and corrected, but the dementia will not itself
21 get significantly better. So an example of that might be
22 a brain tumor, a head injury, or a stroke. In fact, today
23 multi-infarct dementias is one of the leading causes of
24 dementia, multiple strokes. If you prevent further strokes
25 from happening, the dementia will be arrested and there

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1 will be no further decline. So that's an arrested dementia.

2 Q. Okay. And then the third paragraph on the screen
3 right now, does that refer to another category of dementia?

4 A. It does. It refers to the irreversible cases of
5 dementia.

6 Q. Okay. And what is meant by an irreversible case of
7 dementia?

8 A. Everything that is not arrestible or reversible.
9 So it's basically all the progressive dementias, which,
10 of course, the bulk of the dementia cases --

11 Q. Okay. Okay. So let me ask you this: Did those
12 three categories cover the waterfront of types of dementia?
13 Reversible, arrested and irreversible?

14 A. They do.

15 Q. Okay. And what category of dementia does Alzheimer's
16 disease fit into?

17 A. Without a doubt, Alzheimer's disease belongs in the
18 category of irreversible dementias.

19 Q. Would one of skill in the art in 1974 have known
20 that?

21 A. Yes.

22 Q. And would one of skill in the art in 1986 have known
23 that?

24 A. Absolutely.

25 Q. Okay. Now let's look at the sentence about

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1 A. I do see that.
 2 Q. Okay. Then it says, They have suggested measures of
 3 improving the higher functions in cases of local brain
 4 damage like tumor, head injury, infarct, et cetera, by
 5 deinhbibitory procedures and re-education of the rest of the
 6 brain.
 7 A. I do see that.
 8 Q. Okay. Does that sound familiar to you? Does that
 9 description sound familiar to you?
 10 A. That's exactly really what was described in great
 11 detail in that chapter we reviewed already.
 12 Q. That chapter talked about deinhbibition?
 13 A. That's right.
 14 Q. There's a reference to specific brain injury, like
 15 tumor, infarct, what do those maladies have to do with
 16 dementia?
 17 A. He has already put them in the category of the
 18 arrested dementias, so these are conditions that cause
 19 arrested dementia as he described earlier in the paper.
 20 So they cause problems with higher cortical functions, but
 21 they don't get progressively worse.
 22 Q. Okay. But do they show the kind of -- the kind of
 23 effect that dementias can have; is that right?
 24 A. That's right.
 25 Q. All right. And the next sentence says, deinhbibition

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1 refers to the facilitation of acetylcholine activity by
 2 giving small daily doses of cholinesterase inhibitors,
 3 neostigmine, galanthamine.
 4 Do you see that?
 5 A. Yes.
 6 Q. What is the reference there?
 7 A. What he's saying is that one could give cholinesterase
 8 inhibitors, such as neostigmine and galanthamine, and
 9 that by doing so, it could bring back the life of the
 10 silent synapses. That's the deinhbibition.
 11 What the cholinesterase inhibitor would do,
 12 it would facilitate acetylcholine and improve the brain
 13 functions through deinhbibition.
 14 Q. All right. Now, Doctor, was this an article about
 15 local brain damage?
 16 A. It was an article about dementia as the title
 17 clearly alluded to and local brain damage as he would
 18 clearly give -- can cause a form of dementia, which he
 19 considered arrested dementia.
 20 Q. And so what do you take this reference to daily
 21 doses of cholinesterase inhibitors like galanthamine to
 22 mean?
 23 A. To me, it's absolutely inherent in this paper
 24 where he's putting this in context that he's suggesting
 25 cholinesterase inhibitors might be tried for treating

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1 dementia, arrested dementia. That one might restore
 2 cortical functions, as has been shown to be the case for
 3 local brain injury.
 4 Q. All right. And progressive dementias include
 5 Alzheimer's disease; is that right?
 6 A. That's right.
 7 Q. Okay. Doctor, if we could go to Slide 59, please.
 8 Skip ahead to 59.
 9 Thank you.
 10 Okay. Doctor, let's talk about some of your
 11 opinions in this case. I have presented you with a
 12 standard for invalidity under the doctrine of
 13 anticipation; is that right?
 14 A. Yes.
 15 Q. And ask you to express an opinion based on that.
 16 A. Yes.
 17 Q. Okay. And is this the standard I provided you with?
 18 A. Yes; it is.
 19 Q. So it's a single prior-art reference that discloses
 20 either expressly or inherently each limitation of a claim
 21 invalidates that claim by anticipation.
 22 Do you see that?
 23 A. I do.
 24 Q. Do you have an opinion about whether using the
 25 sciences of ordinary skill in 1986, the Bhasker article

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1 A. Yes, it does.
2 Q. Why do you say that?
3 A. Because as we just walked through it, it talked
4 about treatment of patients with progressive dementia,
5 which includes Alzheimer's disease. It's inherent in that.
6 Q. All right. And referring to the administration to a
7 patient suffering from such a disease, an amount of
8 galanthamine. Does Bhasker make reference to that part of
9 the claim?
10 A. He clearly does. He talks about administering -- he
11 talks about administering small daily doses of
12 cholinesterase inhibitors, including galanthamine.
13 Q. All right. Okay. And does Bhasker make reference
14 to administering a therapeutically effective amount of
15 galanthamine?
16 A. Yes, he does.
17 Q. And in what way do you believe that Bhasker says
18 that?
19 A. Well, I think it's -- again, sort of inherent. He's
20 talking about improving cortical functions. And so that
21 is a therapeutically effective amount sufficient to improve
22 brain functions.
23 Q. Okay. And would one of skill in the art in 1986,
24 based on your review of the art concerning galanthamine,
25 have known what a therapeutically effective amount of

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1 galanthamine would be?
2 A. Yes.
3 Q. Okay. So, Doctor, in sum, based on that definition
4 of the standard of anticipation, do you believe that
5 Claim 1 of the '318 patent is anticipated by the Bhasker
6 reference?
7 A. Yes, I do.
8 Q. Okay. All right. Have you also arrived at an
9 opinion concerning obviousness, Dr. Levy?
10 A. I have.
11 Q. Okay. Let's go to the next slide.
12 And have I provided you with some standards
13 concerning obviousness as well?
14 A. You have.
15 Q. Okay. And this is straight from Section 103(a) of
16 the Patent Code, the differences between the subject
17 matter sought to be patented and the prior art are such
18 that the subject matter as a whole would have been
19 obvious at the time the invention was made to a person
20 having ordinary skill in the art to which said subject
21 matter pertains.
22 You understand that is the standard for
23 obviousness?
24 A. I do.
25 Q. All right. Now let's go to the next slide.

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1 doubt.

2 It was clearly -- there was a huge amount of
3 support for a cholinergic deficit hypothesis that the
4 deficiency of acetylcholine contributes to the symptoms.
5 This was hugely investigated, lots of support for that idea.

6 And then we had the studies from physostigmine
7 and tacrine and multiple studies from really leading
8 investigators in the field, showing that there can be
9 positive effects in patients with Alzheimer's disease
10 that you could measure that occasionally they would be
11 clinically significant. Not always, and that these
12 effects were certainly not a home run like we talked about,
13 but there were certainly still positive benefits.

14 And then we had that proof of principle from
15 two different drugs in the class, physostigmine and tacrine.

16 For those reasons, I think one had very
17 reasonable expectation of success that you could use a
18 drug, galanthamine, that was already known to have all the
19 properties and more that also had been compared through
20 its use in Eastern Europe with physostigmine and known to
21 be safe, really well tolerated. Dosing was known. It was
22 very effective to the point that, for the first time, we
23 were seeing people recording benefits on cognitive
24 abilities from the work of Luria, Pernov and Daskalov, all
25 those groups. Hundreds of patients.

1 refer to?

2 A. The acetylcholinase inhibitor as well as the nicotinic

3 allosteric modulator.

4 Q. Do you agree with Dr. Coyle that the dual mechanism

5 of that action remain unsettled?

6 A. I do.

7 Q. Let's go to the next slide, please. The next

8 unexpected benefit that plaintiffs raise is, experts

9 raise, is reduction of caregiver burden slash distress.

10 Are you familiar with plaintiffs allegations

11 in this regard?

12 A. Yes, I am.

13 Q. What do you understand plaintiffs' experts to be

14 saying in this regard?

15 A. The allegation is that by treating the patient with

16 Alzheimer's disease, that the caregivers had a reduced

17 burden and that reduced burden is actually an unexpected

18 reduced burden.

19 Q. Do you agree that a reduced burden to a caregiver is

20 an unexpected benefit of an Alzheimer's disease treatment?

21 A. After caring for nearly a thousand patients a year,

22 the answer is definitely no.

23 Q. Okay. Why do you say that that is not an unexpected

24 benefit?

25 A. There are all sorts of things that contribute to

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1 They can improve behavioral symptoms and they can improve

2 overall functionability.

3 It's obviously, to me, and I think anybody

4 skilled in the art that if you -- if you reduce the

5 symptoms, the cognitive symptoms that we just went through

6 and somebody can stay home alone or not wander off, that's

7 going to reduce caregiver burden.

8 So I think that's a very anticipated benefit.

9 Q. Okay. And actually, are there articles in the art

10 that indicate that caregiver burden is reduced when

11 cholinesterase inhibitors are given to Alzheimer's

12 patients?

13 A. Yes. I think this has been demonstrated through

14 all the cholinesterase drugs. One can measure the positive

15 effects on caregiver burden.

16 Q. All right. Let's look at DX-580, please.

17 And can you identify that document for the

18 record, please?

19 A. Yes. This is abstract entitled Donepezil reduces

20 the time caregivers spend providing care: Results of a

21 one-year, double-blind randomized trial in patients with

22 mild to moderate Alzheimer's disease. As authors are Mastey

23 and others.

24 Q. American Journal of Geriatric Psychiatry?

25 A. Right. In an abstract published in 2001.

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1 caregiver burden. I mean, this is the thing that makes

2 this disease absolutely devastating, that's why it's a

3 16-hour day for caregivers. People with Alzheimer's need

4 constant supervision when it gets severe. That could be

5 for a variety of reasons. Cognitive loss is certainly

6 one example of caregiver burden.

7 For example, the patient who cannot stay home

8 alone because they don't know how to pick up a phone and

9 call if they need help or if they're concerned they might

10 wander out of the house and get lost because of their

11 cognitive disabilities, that provides tremendous caregiver

12 burden because they've got to provide round the clock

13 supervision.

14 Similarly, I think it was alluded to earlier,

15 behavioral problems are the greatest reason that people

16 end up in a nursing home. When somebody has behavioral

17 problems and they can no longer even be managed at home,

18 that leads to institutionalization. That also is a huge

19 source of caregiver burden.

20 Functionally, people may have functional

21 impairment when -- for example, they need help dressing

22 or they need help toileting. That again provides

23 additional caregiver burden.

24 What we know with these drugs is that they

25 improve symptoms. They can improve cognitive symptoms.

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1 A. That's right.
2 Q. He showed that by blocking the muscarinic receptors,
3 there was an amnesia induced in normals that seemed to
4 resemble Alzheimer's patients?
5 A. It seemed to resemble age associated memory loss, not
6 Alzheimer's.
7 Q. That's what was referred to as the scopolamine model
8 for Alzheimer's?
9 A. Or the scopolamine model for geriatric memory loss.
10 Q. Was, in fact, scopolamine used as a model for testing
11 Alzheimer's drugs?
12 A. I believe it was.
13 Q. The focus again was on the muscarinic receptors?
14 A. That's right.
15 Q. As you mentioned, there are two families, the
16 nicotinic family and the muscarinic family?
17 A. That's right.
18 Q. And the focus was on the muscarinic family?
19 A. Yes.
20 Q. In fact, your research which you conducted in the
21 late eighties and nineties, focused considerably on the
22 muscarinic receptors?
23 A. That's right.
24 Q. You were, in fact, involved with Lily in the
25 development of xanomeline?

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1 A. Yes.
2 Q. Xanomeline was a drug that was intended to overcome
3 the cholinergic deficit in Alzheimer's disease?
4 A. Correct.
5 Q. The goal, much like what was achieved with
6 galanthamine, was to improve patient symptoms by
7 overcoming their cholinergic deficit?
8 A. That's right.
9 Q. And your idea that you worked with Lily on was to
10 directly stimulate the muscarinic receptor; correct?
11 A. That's right.
12 Q. In fact, you were very specific you intended to
13 stimulate a particular type of muscarinic receptor?
14 A. That's right.
15 Q. So you very deeply focused down on the muscarinic
16 receptor; is that correct?
17 A. That's right.
18 Q. And that was induced in large part because of this
19 link between the muscarinic receptors and memory; is that
20 correct?
21 A. That's right.
22 Q. And Lily took it all the way through large-scale
23 phase three trials; correct?
24 A. They did.
25 Q. Now, in the late nineties, it failed. It was not

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1 approved as a treatment for Alzheimer's; correct?
2 A. It -- I would couch that. I would say it failed in
3 terms of FDA approval but it didn't fail as a -- as
4 positively improving symptoms in patients with Alzheimer's
5 disease.
6 Q. It had certain side effect problems?
7 A. That's right.
8 Q. And it's not used as a treatment for Alzheimer's
9 disease?
10 A. That's right.
11 Q. And from Lily's perspective of having spent half a
12 billion dollars on clinical trials, it was a failure?
13 A. That may be the case.
14 Q. The thing I really want to focus on is this model of
15 the cholinergic deficit was a memory-driven model; is that
16 correct?
17 A. Yes, it was.
18 Q. And it was focused on the muscarinic receptors;
19 correct?
20 A. It was.
21 Q. Now, the other thing that we hadn't really shown in
22 your diagram --
23 A. If I could just -- I didn't quite finish the answer.
24 It was memory-driven but also from knowledge of humans,
25 blocking muscarinic receptors specifically caused more

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1 than just memory loss. It caused confusions,
2 hallucinations, behavioral problems, all sorts of
3 cognitive impairment beyond just memory loss.
4 Q. But the focus was on muscarinic receptor?
5 A. That's right, because blockers of nicotinic receptors
6 didn't really have any pronounced effects at that time.
7 Really the field, state of the art in 1986, was the vast
8 majority of people thought that muscarinic receptors, the
9 preponderance of evidence was that muscarinic receptors
10 was the class that was most important for the symptomology
11 of Alzheimer's disease.
12 Q. The conventional wisdom was to focus on the muscarinic
13 receptors?
14 A. That's correct.
15 Q. The other thing this diagram isn't really showing,
16 the cholinergic system exists throughout the body and the
17 brain?
18 A. Correct.
19 Q. Your muscles, do they rely on the cholinergic system?
20 A. Yes.
21 Q. That's their nicotinic receptor?
22 A. And the muscarinic receptor as well.
23 Q. The neuromuscular junction, are you familiar with
24 that?
25 A. Yes.

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1 Q. Is that a nicotinic receptor?

2 A. Predominantly nicotinic, but it has muscarinic

3 aspects.

4 Q. The gut has cholinergic receptors in it?

5 A. That's correct.

6 Q. Are those predominantly muscarinic?

7 A. It's mixed, but many muscarinic effects in the gut.

8 Q. Cholinergic effects can have effects in the body and

9 the brain?

10 A. Yes.

11 Q. Alzheimer's disease is just the brain?

12 A. That's right.

13 Q. And you mentioned that physostigmine had a problem

14 with peripheral cholinergic side effects; is that correct?

15 A. That's right.

16 Q. The problem is that cholinesterase is in the body

17 and the brain, too; is that correct?

18 A. That's right.

19 Q. And so when you give physostigmine, it doesn't just

20 inhibit it in the brain, it inhibits it in the body and the

21 gut. All through the body; correct?

22 A. That's right.

23 Q. And when you inhibit cholinesterase where you don't

24 want to, it causes problems; is that correct?

25 A. It has a potential to. That's right.

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1 Q. In trying to treat Alzheimer's disease, particularly

2 in light of the problems with physostigmine, what people

3 in the art wanted to do was to find a cholinesterase

4 inhibitor that worked in the brain but not so much in the

5 body; is that correct?

6 A. Or to block the effects that occur elsewhere.

7 Q. By administering some other drug?

8 A. That's what was done in all those trials. For

9 example, people were administered N methyl scopolamine

10 so that you could block the cholinesterase effects in

11 the peripheral tissues and avoid some of those problems.

12 Q. Sometimes the cholinesterase inhibitor can be given

13 with something to block the unwanted effects?

14 A. That's right.

15 Q. For example, when physostigmine, as a cholinesterase

16 inhibitor, is giving to treat curare poisoning?

17 A. Yes.

18 Q. All you want from the physostigmine in that case is

19 the nicotinic effects.

20 But when you want to treat Alzheimer's disease,

21 the thought was to find a cholinesterase inhibitor that

22 acted predominantly in the brain and not in the body?

23 A. That would be the ideal objective.

24 Q. Peripheral cholinergic effects were undesirable?

25 A. Correct.

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1 Q. Now, I think you testified that galanthamine was used

2 principally for myasthenia gravis before 1986; is that

3 correct?

4 A. I don't know if it was principally, but I know the

5 articles I read, like Pernov, Pernov's specialty was in

6 muscle diseases, so he described over 100 patients with

7 muscle diseases, myasthenia gravis. Others used it

8 predominantly for other types of conditions.

9 Q. You've relied on Pernov, so let's see what Pernov

10 says.

11 MR. SIPES: If we could pull up Plaintiffs'

12 Exhibit 1181...

13 BY MR. SIPES:

14 Q. I believe you should still have it in front of you.

15 A. I will in a minute.

16 (Pause.)

17 THE WITNESS: Okay.

18 BY MR. SIPES:

19 Q. If you will turn to the second page of Pernov under

20 clinical observations. I think that's what you were

21 citing to.

22 A. That's right.

23 Q. Let's turn to the second page.

24 MR. SIPES: If you could just blow it up, the

25 first paragraph under clinical observations... That one.

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1 BY MR. SIPES:

2 Q. What does he say in the first sentence about clinical

3 observations?

4 A. Nivalin's therapeutic range of application above all

5 encompasses diseases of the neuromuscular apparatus --

6 myasthenia gravis, dystrophia, et cetera, and diseases of

7 the periphmotic neuron. Paresis and paralis. Used to

8 treat some diseases which affect the central motor neuron.

9 Infantile cerebral palsy, multiple sclerosis.

10 Q. Nivalin again is galanthamine?

11 A. Yes.

12 Q. So the indication, the therapeutic range that Pernov

13 is teaching for galanthamine, is above all, that's his

14 word, above all, for diseases of the neuromuscular

15 apparatus. Peripheral diseases?

16 A. That's right.

17 Q. So what Pernov was saying was that galanthamine has

18 a lot of activity in the periphery; is that correct?

19 A. That's right.

20 Q. And in terms of the type of activity he's pointing

21 to, myasthenia gravis is nicotinic; correct?

22 A. Right. The symptoms of the neuromuscular apparatus

23 were nicotinic. The central motor neurons I suspect are

24 largely muscarinic.

25 Q. Above all the indications of nivalin, it's

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1 peripheral --
 2 A. It's peripheral musculature.
 3 Q. In terms of a person in 1986 reading this, they would
 4 see it as being above all peripheral and nicotinic?
 5 A. Definitely, I would agree.
 6 Q. If we turn to the next page, or actually the page
 7 after that, and the middle paragraph I think is what you
 8 referred to.
 9 A. 5986?
 10 Q. 5986. Correct. That will -- this issue of the
 11 central motor neuron that you pointed to. In fact, what
 12 Pernov says is, the findings of treating diseases involving
 13 the central motor neuron, a total of 64 cases in all, are
 14 less straightforward; correct?
 15 A. That's right.
 16 Q. So the ones that are above all indicated Pernov are
 17 peripheral nicotinic.
 18 I want to take a look at what the art was saying
 19 about this.
 20 (Pause.)
 21 MR. SIPES: If I could approach...
 22 THE COURT: Certainly.
 23 (Mr. Sipes handed an exhibit to the witness.)
 24 BY MR. SIPES:
 25 Q. Actually, I will ask you to take a look at Plaintiffs'

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1 Exhibit 653.
 2 A. Okay.
 3 Q. This is an article published in Science magazine in
 4 1982 by Raymond Bartus and others entitled The Cholinergic
 5 Hypothesis of Cholinergic -- do you see that?
 6 A. Yes.
 7 Q. You've seen this article before?
 8 A. Yes.
 9 Q. In fact, you've cited in article in your expert
 10 reports as a particularly influential article when it was
 11 given, did you not?
 12 A. I think it is, yes.
 13 Q. In fact, you indicated, you went and researched it,
 14 it has been cited over 3,000 times, almost 300 times by
 15 1986; is that correct?
 16 A. I don't remember those numbers.
 17 Q. And Mr. Bartus or Dr. Bartus, I should say, was a
 18 leading figure in Alzheimer's disease?
 19 A. Definitely. A leading researcher in memory loss in
 20 acetylcholine.
 21 MR. SIPES: I move the admission of Plaintiffs'
 22 Exhibit 653.
 23 MR. LOMBARDI: No objection.
 24 THE COURT: Thank you.
 25 DEPUTY CLERK: So marked.

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1 *** (Plaintiffs' Exhibit No. 653 was received into
 2 evidence.)
 3 BY MR. SIPES:
 4 Q. Why don't we begin, if you will turn to Page 414 of
 5 this article. And if we could blow up under Directions
 6 for Future Research, the title Directions for Future
 7 Research and the first half of the patent.
 8 Okay. So Dr. Bartus sets forth in his
 9 article some directions for future research, does he not?
 10 A. Yes, he does.
 11 Q. And he begins by noting, a question that is beginning
 12 to emerge is why different cholinomimetics seem to produce
 13 different results on memory in geriatric subjects.
 14 Do you see that?
 15 A. I do.
 16 Q. Again, you testified that cholinomimetics,
 17 that would be a term that encompassed cholinesterase
 18 and other --
 19 A. Not all cholinergic agents. Only those that affect --
 20 Q. Agents that enhance cholinergic effects?
 21 A. Yes. _____
 22 Q. It would certainly include cholinesterase inhibitors?
 23 A. Definitely.
 24 Q. It would certainly include xanomeline?
 25 A. That's right.

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1 Q. And he's noting that there have been very inconsistent
 2 results with trying cholinomimetics, is he not?
 3 A. He is.
 4 Q. And he's, in fact, reviewed studies of cholinomimetics
 5 in Alzheimer's patients?
 6 A. Yes.
 7 Q. He has seen inconsistent results?
 8 A. Yes.
 9 Q. He's noting, for example, the absence of clear
 10 positive effects of choline and Lecithin on geriatric
 11 patients?
 12 A. Yes.
 13 Q. Those were the precursor theory?
 14 A. Yes.
 15 Q. He finds that perplexing, does he not?
 16 A. Apparently he did.
 17 Q. But then he reaches a conclusion based on all of the
 18 evidence. He says, among the many possible explanations,
 19 one that is consistent with all available data is that the
 20 more directly one stimulates the muscarinic receptor, the
 21 more robust and consistent are the effects on memory
 22 performance in aged subjects; correct?
 23 A. That's right.
 24 Q. So he is recommending a focus on stimulating as
 25 directly as possible the muscarinic receptor; is that

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1 correct?
2 A. I'm not sure he's saying focus on that exclusively.
3 I think he's saying one might expect more pronounced
4 effects.
5 Q. That would lead in the direction of muscarinic agonist
6 to --
7 A. That's right.
8 Q. It would certainly lead away from agents that were
9 weak muscarinic agents; correct?
10 A. That's definitely true.
11 Q. And, in fact, let's see what he says about agonists
12 versus physostigmine.
13 If you could turn with me to the bottom of
14 the page before 413...
15 Now, you'll note, this is in a section which
16 he refers to as facilitation --
17 A. Yes.
18 Q. That's his review of the work on agonists and
19 precursors; correct?
20 A. For geriatric memory.
21 Q. Correct.
22 Q. On the right-hand column at the bottom, he notes
23 that in addition to physostigmine, the muscarinic agonist
24 arecoline --
25 A. Yes.

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1 Q. After receiving a single injection of arecoline,
2 young adult volunteers exhibited significant improvement
3 in ability to recall recently learned verbal material.
4 Do you see that?
5 A. I do.
6 Q. Then he notes, short-term doses of arecoline can
7 also enhance perform performance on a memory test in aged
8 monkeys and Alzheimer's patients?
9 A. That's right.
10 Q. He says in the monkey study, direct comparisons
11 revealed that the effects of arecoline were more robust
12 and less variable than when the same monkeys were tested
13 under either physostigmine or choline; correct?
14 A. I see that.
15 Q. So Dr. Bartus, in his highly influential science
16 article, was saying that the results on arecoline in
17 Alzheimer's patients and in animal tests were more
18 promising than with cholinesterase inhibitors; is that
19 correct?
20 A. I'm not sure he said more promising.
21 Q. He says more robust and less variable.
22 A. That's right.
23 Q. Would that be a good thing or a bad thing?
24 A. That would be a good thing.
25 Q. So I think we can agree that he's saying that direct

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1 young monkeys.

2 Do you see that?

3 A. Yes.

4 Q. He says, in addition, scopolamine's age-mimicking
5 effects on memory were shown to be at least somewhat specific
6 to its effects on central muscarinic receptors, since similar
7 age-like effects on memory were not obtained with a number of
8 other drug treatments, including dopaminergic and alpha-
9 adrenergic blockers, several nonspecific and
10 catecholaminergic stimulants, nicotinic receptor blockers,
11 and peripheral anticholinergics?.

12 A. Yes.

13 Q. This emphasizes what you've testified to. That the
14 focus in 1986 was on the central muscarinic receptor; is
15 that correct?

16 A. That's right.

17 Q. In fact, the study which had shown no similar
18 effects from blocking nicotinic receptors led away from
19 drugs that would be weak muscarinic agents and might focus
20 on the nicotinic system?

21 A. I think that's fair.

22 Q. And then if you will look to current status of
23 treatment approaches, the section on Page 343. If you
24 look at the top paragraph, he reviews the current status of
25 efforts to treat Alzheimer's disease by cholinomimetics,

1 Q. In fact, not only does galanthamine not have
2 specificity for its -- its use above all in the literature
3 had been for peripheral nicotinic effect, myasthenia
4 gravis?

5 A. That's right.

6 Q. So galanthamine is in the exact opposite direction
7 from what Dr. Bartus is saying in his article; correct?

8 A. I don't think that's really a fair assessment. It
9 was known that galanthamine had muscarinic and nicotinic
10 properties.

11 Q. But it was not specific for muscarinic effect?

12 A. That's right. For sure.

13 Q. And it had, in fact, significant other effects,
14 including nicotinic effects; correct?

15 A. That's right. Like all cholinesterase inhibitors.

16 Q. Certainly from where the art was, one wouldn't go
17 to a weak muscarinic agent; is that correct?

18 A. Probably not. You'd really want to avoid the side
19 effects. That's really what he was talking about, not
20 dealing with potency. The side effects.

21 Q. If something is a weak muscarinic agent, then all
22 its other side effects are going to be weak?

23 A. Depending on the dose.

24 (Pause.)

25

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1 article.
2 The bottom of the left-hand column, that
3 paragraphs begins, Acetylcholinesterase inhibitors show
4 more promise as a treatment strategy in senile dementia
5 of the Alzheimer's type than pre-synaptic agents, perhaps
6 because they do not require pre-synaptic neurons to augment
7 the synthesis of acetylcholine.
8 A. Yes.
9 Q. By pre-synaptic agents, what doctor Johns is
10 referring to is precursors like choline and Lecithin, is
11 that correct?
12 A. That's right.
13 Q. So she's basically saying they're better than the
14 precursors which did nothing, is that correct?
15 A. That's right.
16 Q. So a way of reading it is saying it's better than
17 nothing?
18 A. Okay.
19 Q. Then she says, both strategies, however, share a
20 fundamental limitation in that they are dependent on an
21 intact pre-synaptic neuron to provide a substrate for
22 their activity.
23 Do you see that?
24 A. I do.
25 Q. What she's saying is that the cholinesterase inhibitor

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1 can't create more acetylcholine in the synapse than is
2 released by the pre-synaptic neuron. It can only help
3 preserve the acetylcholine that's released?
4 A. That's absolutely right.
5 Q. She refers to that as a limitation on cholinesterase
6 inhibitor to treat Alzheimer's disease?
7 A. She refers to that. It's clearly a limitation.
8 A potential limitation.
9 Q. That was recognized in the art in 1986?
10 A. Yes.
11 Q. These problems may be circumvented by administering
12 cholinergic agents which work directly at post-synaptic
13 receptor sites, since the number of post-synaptic
14 muscarinic binding sites is not reduced in SDAT patients
15 as compared to age matched controls?
16 A. Yes.
17 Q. She's suggesting one of the limitations could be
18 avoided in treating Alzheimer's disease by instead using
19 a direct muscarinic agonist?
20 A. That's correct.
21 Q. The approach that, in fact, you took, is that
22 correct?
23 A. That's one of the approaches. Correct.
24 Q. And she notes in fact that, going further down,
25 that significant cognitive improvement was also measured

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1 Q. It failed; correct?

2 A. It failed to reach FDA approval, that's right.

3 Q. Is it considered today a treatment for Alzheimer's

4 disease?

5 A. Today it's not considered a treatment for Alzheimer's

6 disease.

7 Q. And when were you given SB-202026 to patients? I

8 believe you have your C.V. in front of you if that will

9 assist you.

10 A. Here it is.

11 (Pause.)

12 - - -

13 A. It was back in 1996 that the trial was performed.

14 Q. In the mid-nineties you were giving SB-202026 to

15 patients to try to develop a treatment for Alzheimer's

16 disease; correct?

17 A. Yes.

18 Q. You were not giving them galanthamine; correct?

19 A. Correct.

20 Q. When were you giving patients xanomeline in order to

21 develop a treatment for Alzheimer's disease?

22 A. That was around that same period of time.

23 Q. The mid-nineties?

24 A. That's right.

25 Q. Both of these, xanomeline and SB-202026, are muscarinic

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1 agents that you were using? It was to overcome the

2 cholinergic deficit in Alzheimer's disease patients?

3 A. Yes.

4 Q. They weren't cures for Alzheimer's disease in all

5 cases. You were attempting to develop a drug to provide

6 alleviation of the cognitive decline; is that right?

7 - - -

8 A. That's right.

9 Q. Now, at this time, did you think there was a need for

10 symptomatic treatment for Alzheimer's disease?

11 A. Definitely.

12 Q. Was there a need for a drug that would address the

13 cholinergic deficit in Alzheimer's disease?

14 A. There was definitely a need to improve the therapy as

15 they talked about. We were far from hitting a home run with

16 available drugs. We had modest benefits and we still had

17 only modest benefits and these were definitely attempts to

18 get better symptomatic benefit.

19 Q. In 1986, there was an even greater need; correct?

20 A. Greater than what?

21 Q. Than in 1996 when at least you had tacrine?

22 A. Okay.

23 Q. Is that correct?

24 A. Sorry?

25 Q. It was a great need for even a symptomatic treatment

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1 for Alzheimer's need?

2 A. Correct.

3 Q. It was a very deeply felt need. There were many

4 people working to try to find even a symptomatic

5 treatment; is that correct?

6 A. That's correct.

7 Q. Many people, for example, had devoted themselves to

8 try precursors in an effort to alleviate the cholinergic

9 deficit?

10 A. Yes.

11 Q. Many people did work with physostigmine in order to

12 alleviate --

13 A. Yes.

14 Q. The invention claimed in the patent here, a treatment

15 for Alzheimer's disease that addresses the cholinergic

16 deficit, that addresses the need that people were looking

17 for in 1986; is that correct?

18 A. I understand.

19 Q. You agree with that?

20 A. I agree.

21 Q. And it has at least in part met that need; correct?

22 A. Which -- any of the cholinesterase inhibitors?

23 Q. Correct.

24 A. Has partially met the need for symptoms. It's not

25 a very poor job. It has met some need.

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1 Q. You prescribed galanthamine and the other --

2 A. Yes.

3 Q. Galanthamine has done a better job than, for example,

4 tacrine?

5 A. That's right.

6 Q. Because you don't have the safety problems here for

7 tacrine?

8 A. That's right.

9 Q. You prescribed galanthamine?

10 A. I do.

11 Q. But you don't prescribe tacrine?

12 A. Correct.

13 Q. You prescribe galantamine more than Exelon?

14 A. Yes.

15 Q. Exelon has some unfortunate side effects; correct?

16 A. It does.

17 Q. It causes a lot of vomiting?

18 A. Causes a lot of gastrointestinal symptoms, more than

19 vomiting.

20 Q. You prefer galanthamine?

21 A. I do.

22 Q. Do you think that the greater tolerability of

23 galanthamine over Rivastigmine, would you expect that

24 before galanthamine was approved in 2001?

25 A. Not really. And I realize this is my anecdotal

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1 experience. It's not scientific evidence in my hands.
 2 I'm just more comfortable using other drugs.
 3 Q. Did you ever, in facts, worry that galanthamine was
 4 going to have possibility for peripheral side effects?
 5 A. I wouldn't have expected serious any more than any of
 6 the other drugs. We already had proof of what other drugs
 7 do. Again from using them for decades.
 8 Q. But, in fact, in your experience, your prescribing
 9 experience, it turned out it has fewer side effects than
 10 Rivastigmine; correct?
 11 A. In my experience, tend to have less, yes, at higher
 12 doses.
 13 Q. In fact, these problems with Rivastigmine with Exelon,
 14 they're widely known?
 15 A. I think a lot of people are aware of them.
 16 Q. This idea that it's less tolerable than galanthamine,
 17 that's widely shared?
 18 A. As I'm thinking widely known, I think many Alzheimer
 19 specialists. In terms of the community of doctors who
 20 prescribe these drugs, I don't think it's widely known.
 21 Q. The fact of the matters --
 22 A. Probably the more experienced suspect that's the
 23 case.
 24 MR. SIPES: Your Honor, if I could approach
 25 the witness...

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1 THE COURT: Yes.
 2 (Mr. Sipes handed documents to the witness.)
 3 BY MR. SIPES:
 4 Q. Dr. Levey, I've handed you Plaintiffs' Exhibit 214,
 5 which is an article by Mohammed Saddiqui and Alan Levey
 6 titled Cholinergic Therapies in Alzheimer's Disease, a
 7 review article published in 1999.
 8 Do you see that?
 9 A. I see that.
 10 Q. Did you, in fact, write this article?
 11 A. I did.
 12 Q. Do you have it on your C.V.?
 13 A. I do.
 14 Q. You tried to be truthful and accurate?
 15 A. Yes, I did.
 16 MR. SIPES: I will move Plaintiffs' Exhibit 214
 17 into evidence.
 18 MR. LOMBARDI: No objection.
 19 THE COURT: Thank you.
 20 DEPUTY CLERK: So marked.
 21 *** (Plaintiffs' Exhibit No. 214 was received into
 22 evidence.)
 23 BY MR. SIPES:
 24 Q. First, let me ask you to turn to the second --
 25 first, let me ask you, this is called cholinergic

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1 therapies in Alzheimer's disease; is that correct?
 2 A. That's right.
 3 Q. Your goal here was to review the status of
 4 cholinergic therapies in Alzheimer's disease?
 5 A. That's right.
 6 Q. These were efforts to address the cholinergic deficit
 7 in Alzheimer's disease?
 8 A. That's right.
 9 Q. And this was a review you did in 1999; correct?
 10 A. That's right.
 11 Q. If you will turn to the second page, on the left-hand
 12 column, the bottom paragraph, which begins, At least 38
 13 acetyl cholinesterase inhibitors are currently being
 14 studied worldwide in pre-clinical or clinical studies; is
 15 that correct?
 16 A. That's right.
 17 Q. Was -- did you believe that to be true when you wrote
 18 that?
 19 A. I certainly did.
 20 Q. So in 1999, there were 38 cholinesterase inhibitors
 21 that were being looked at as possible treatments for
 22 Alzheimer's disease; is that correct?
 23 A. That's right.
 24 Q. And there are four approved today; correct?
 25 A. That's right.

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1 Q. And of those four, one of them, which had been
 2 approved before your article, is not prescribed because
 3 it's not safe; is that correct?
 4 A. That's right.
 5 Q. And of the remaining three, one of them, Rivastigmine,
 6 people with experience in treating Alzheimer's disease
 7 find to have tolerability problems; is that correct?
 8 Is it fair to say that finding the right
 9 cholinesterase inhibitor has not proven to be easy?
 10 A. I think it's fair to say that many people have jumped
 11 on the bandwagon, are trying to develop cholinesterase
 12 inhibitors that are going to overcome the limitations of
 13 the existing ones.
 14 Q. Many of them have failed?
 15 A. Many are still ongoing. For example, some of the
 16 ones we talked about here, Ruperzine A, the Alzheimer
 17 disease study group of all the Alzheimer groups in the
 18 country, this is a drug that still should be studied.
 19 Q. How long has Ruperzine A still been studied?
 20 A. It's in clinical trials now.
 21 Q. Do you know clinical trials have been going on for
 22 almost 20 years?
 23 A. The NIH -- phase three trial is just ongoing now.
 24 Q. But there are many prior clinical trials for it?
 25 A. Yes.

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1 A. That's right.

2 Q. You're talking here about the behavioral benefits
3 that you talked about in your direct testimony from
4 cholinesterase inhibitors?

5 A. That's right.

6 Q. In 1999, you described those behavioral benefits as
7 surprising and dramatic; is that correct?

8 A. That's right. More surprising than I think the
9 general readership would expect.

10 Q. There were other cholinergic attempts that were made
11 in addition to muscarinic agonists and -- muscarinic
12 agonists and cholinesterase inhibitors?

13 A. Okay.

14 Q. You refer, for example, to acetylcholine releasers?

15 A. That's right.

16 Q. That's a pre-synaptic approach?

17 A. That's correct.

18 Q. So it's not correct to say that in 1986, the
19 pre-synaptic approach was dead; is that correct?

20 A. Definitely not. I would say almost no approach has
21 been dead. Remember, there's no cure. People were trying
22 lots of things.

23 Q. There were many different ways being tried, even
24 back in 1986, to try to address the cholinergic deficit
25 of Alzheimer's disease; is that correct?

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1 A. That's right.

2 Q. And logic led in a lot of different directions;
3 correct?

4 A. I think that's fair.

5 Q. And people who worked on muscarinic agonists thought
6 that was the promising way to go; is that correct?

7 A. I certainly did.

8 Q. And people who worked on acetylcholine thought that
9 was the logical way?

10 A. One of the logical ways. Lots of thing can be
11 pursued in parallel. It's a tough disease.

12 Q. It's a tough disease. Correct.

13 Q. It's a tough disease?

14 A. Yes.

15 Q. There was no right way to address the cholinergic
16 deficit?

17 A. I think the consensus was many ways should be
18 approached. That was all the consensus about, it's
19 reasonable to try everything that has some scientific
20 rationale.

21 Q. Reasonable to try everything?

22 A. That has scientific rationale.

23 Q. Which included precursors, cholinesterase inhibitors?

24 A. The more scientific rationale, the more reasonable.

25 Q. And you thought the most reasonable was direct

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1 muscarinic agonists?

2 A. I think it had some advantages and I think all of
3 them have their own pros and cons like I do today. So I
4 think until we have a cure, we have to address all the
5 possible pros and cons and do our best.

6 MR. SIPES: Your Honor, if I could approach the
7 witness...

8 THE COURT: All right.

9 (Mr. Sipes handed an exhibit to the witness.)

10 BY MR. SIPES:

11 Q. Dr. Levey, I have handed you Plaintiffs' Exhibit
12 1223, which is a publication by you and a couple of
13 co-authors, Donna Flynn, Gabby Ferraro DeLeo and Deborah
14 Flash, entitled differential alterations in muscarinic
15 receptor subtypes in Alzheimer's disease. Implications
16 for cholinergic based therapies published in 1995.

17 Do you see that?

18 A. I do see that.

19 Q. Did you, in fact, are you an author of this article?

20 A. I am.

21 Q. And you list it on your C.V.?

22 A. I do.

23 Q. And you tried to be truthful and accurate?

24 A. I did.

25 MR. SIPES: I'd move Plaintiffs' Exhibit 1223.

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1 MR. LOMBARDI: No objection.

2 THE COURT: Thank you.

3 DEPUTY CLERK: So marked.

4 *** (Plaintiffs' Exhibit No. 1223 was received into
5 evidence.)

6 BY MR. SIPES:

7 Q. First, let me ask you to turn to the summary, really,
8 the last sentence of the summary.

9 Now, this was written in 1995; is that correct?

10 A. That's right.

11 Q. The only approved cholinergic therapy at the time was
12 tacrine; correct?

13 A. I believe that's correct.

14 Q. Now, you state at the end of your summary that your
15 findings with regard to muscarinic receptors suggests one
16 possible explanation for the relative ineffectiveness of
17 cholinergic replacement therapies used to date and suggest
18 suspension and new directions for development of effective
19 therapeutic strategies for AD?

20 A. That's right.

21 Q. So you thought that tacrine was relatively
22 ineffective; is that correct?

23 A. Not as effective as one would have liked, for sure.

24 Q. I think your term was relative ineffectiveness;
25 correct?

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1 A. Okay.

2 Q. And if you look on the second page, you have a

3 section cholinergic neurotransmission, focus of therapeutic

4 interventions. If we could look at the second paragraph of

5 that...

6 First, you note, over the past ten years, our

7 laboratory has studied the role of the cholinergic system

8 in pathogenesis and progression of Alzheimer's disease.

9 We have specifically focused on the muscarinic

10 acetylcholinic receptors since they are the primary targets

11 of any cholinergic replacement therapies. Is that true?

12 A. Yes. It was then.

13 Q. They're the primary targets in the brain?

14 A. Certainly from that perspective.

15 Q. The line timeline for the last ten years, that would

16 be from 1985 on?

17 A. That's right.

18 Q. Now, you say our laboratory. You weren't working

19 on that in 1985, or were you?

20 A. No. Really I think our laboratory referred to the

21 person who actually was the primary author, Donna Flynn,

22 at another university. I think that's where the 1985 came

23 from.

24 Q. You were still a resident in 1985?

25 A. That's right.

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1 Q. And when did you start to focus on muscarinic

2 receptors and treatment strategies?

3 A. About 1990, '91.

4 Q. The -- the next section is muscarinic receptors in

5 Alzheimer's disease early studies.

6 Do you see that? That's the next paragraph.

7 A. What page are you on?

8 Q. The same page.

9 A. Sorry.

10 Q. The next section. Do you see it's entitled Muscarinic

11 Receptors in Alzheimer's Disease: Early Studies?

12 A. Yes.

13 Q. And then the sentence, however, in 1985 we

14 re-examined the status of muscarinic receptors in

15 Alzheimer's disease in light of emerging evidence

16 for at least two distinct populations of sites, M-1 and

17 M-2, in the brain with different affinities for agonists.

18 Do you see that?

19 A. I do.

20 Q. Our studies demonstrated a selective loss of

21 pre-synaptic M-2 sites and a relative sparing of the

22 post-synaptic M-1 sites in Alzheimer's disease.

23 Do you see that?

24 A. Yes.

25 Q. You're referring to a publication by Professors Nash

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1 and Flynn in 1985?

2 A. That's right

3 Q. You say these findings, that 1985 paper, is that

4 correct?

5 A. That's correct.

6 Q. Suggested that non-receptor subtype selected

7 therapies may not be beneficial since their -- do you

8 see that?

9 A. I do see that.

10 Q. That's quite a mouthful, but non-receptor subtype

11 selected therapies we've already discussed, that would

12 include cholinesterase inhibitors?

13 A. That would.

14 Q. What you are saying, the findings in 1985 about

15 M-1 and M-2 receptors suggested that cholinesterase

16 receptors may not be beneficial since their action at

17 pre-synaptic auto receptors may inhibit further --

18 A. That's correct. Again, it's -- these drugs were

19 not very effective and so the question is, is that one of

20 the things contributing to limiting the effectiveness.

21 Q. Your term, in fact, was may not be beneficial in

22 1985?

23 A. That certainly was written there. That's right.

24 Q. That's a rather deep skepticism of cholinesterase

25 inhibitors in 1985?

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1 A. Of any drugs that stimulate all the receptors

2 simultaneously, the effects may not be as effective as

3 perhaps possible with the selective drug.

4 Q. I understand today what you'd like to say as

5 effective.

6 A. What I'm comparing it to, if one were able to

7 stimulate one receptor versus all receptors, that's what

8 the relative effectiveness is or the limited effectiveness

9 is.

10 Q. What you wrote, it suggests in 1985, the

11 cholinesterase inhibitors may not be beneficial.

12 A. I realize that.

13 Q. Then you wrote, thus, the pharmaceutical industry

14 began to focus on the development of M-1 selective agonists

15 and M-2 receptor agonists?

16 A. That's right.

17 - - -

18 Q. You wrote in 1985 that the pharmaceutical industry

19 began to focus in attempting to address the cholinergic

20 deficit in Alzheimer's disease with M-1 selective agonists

21 and M-2 selective agonists?

22 A. It doesn't say exclusively. Clearly as we go, the

23 pharmaceutical industry continued to work on other avenues of

24 cholinergic deficits.

25 Q. What you wrote was that the pharmaceutical industry

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1 began to focus on them; correct?

2 A. That's right.

3 - - -

4 A. That's right.

5 Q. And it's certainly correct, for example, that
6 muscarinic M-1 selective muscarinic agonists looked
7 promising?

8 A. I think they did at that time, that's right.

9 Q. And there was starting to be a lot of focus on those;
10 correct?

11 A. That's right.

12 Q. And we saw, for example, the influential Dr. Bartus
13 was recommending muscarinic agonists?

14 A. That's right.

15 Q. Let me ask you -- we've marked the patent in the
16 case. If you could look at the their '318 patent,
17 Plaintiffs' Exhibit 1...

18 Let's look on Column 1, the first -- the
19 paragraph that begins at Line 11. Further down.

20 Do you see that? That's a discussion of two
21 papers by Cozanitis; correct?

22 A. Yes.

23 Q. And you've reviewed those papers, have you not?

24 A. I have.

25 Q. In fact, I think you said that you are relying on a

1 galanthamine and neostigmine?
2 A. That's what he says in the next sentence.
3 Q. Both cholinesterase inhibitors?
4 A. That's correct.
5 Q. He says, first, the central action of galanthamine.
6 Do you see that?
7 A. I do.
8 Q. That's referring to the fact that neostigmine acts only
9 on the periphery. Physostigmine both on the --
10 A. It refers to neostigmine acts preferentially on
11 the periphery.
12 Q. Second, the fact that physostigmine, according to
13 Salvini, Frosali and Facetti, is 20 times more potent.
14 A. I see that.
15 Q. Which is another way of saying galanthamine is 20
16 times less potent than neostigmine?
17 A. That's correct.
18 Q. Is that an accurate of accurate statement of
19 galanthamine's potency?
20 A. I can't vouch for that. That's what he says.
21 Q. Third, that due to the very slight muscarinic effect
22 of galanthamine, no atropinization is necessary.
23 Do you see that?
24 A. I see that.
25 Q. So Professor Cozanitis is describing galanthamine as

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1 having very slight muscarinic effect?
2 A. Yes.
3 Q. He's describing it as having predominantly nicotinic
4 effect?
5 A. I don't see him saying that.
6 Q. Well, what effect do you understand galanthamine to
7 be if its muscarinic effect is very slight?
8 A. I think he's just saying it has slight muscarinic
9 effects.
10 Q. He's describing it as a weak muscarinic agent?
11 A. Right.
12 Q. Let me show you one more (handing exhibit to the
13 witness).
14 I've handed you a copy of Plaintiffs' Exhibit
15 1350 entitled Clinical Experiences with a New Curare
16 Antidote Galanthamine. Are you familiar with this article?
17 A. No.
18 Q. Did you review the prosecution history in this case?
19 A. I did.
20 Q. But you don't recall whether Stojanov was cited in the
21 prosecution of the patent?
22 A. I don't remember that.
23 Q. Okay. In any event, you recognize this as an
24 article on galanthamine that would be accessible to a
25 person of ordinary skill in the art?

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1 previous paper, for example, I don't remember what effect
 2 they are actually measuring, I don't think you mentioned
 3 it, and I don't know off the top of my head. Here they
 4 are talking about a specific curare effect and this
 5 contrasts a little bit with some of the results that some
 6 of the other in this group shows where they thought the
 7 most potent effects were actually seen for cognition, like
 8 memory.
 9 Q. Well, first, what you are saying is that the balance
 10 of nicotinic and muscarinic effects of an agent will depend
 11 upon the particular use you're putting into?
 12 A. Yes. I'm saying depending on what you're measuring,
 13 you may see different effects.
 14 Q. But he's saying that its muscarinic effects are
 15 slight?
 16 A. For what he's measuring.
 17 Q. What he's measuring are nicotinic effects?
 18 A. Yes.
 19 Q. He's finding that the nicotinic effects outweigh the
 20 muscarinic effects?
 21 A. Yes.
 22 Q. He described the muscarinic effects as slight?
 23 A. That's right.
 24 Q. Now, are there cognitive effects of nicotinic in the
 25 brain?

1 A. And synapse loss and neuron loss and chemical changes.)
 2 We view all of those as parts of the pathological changes.
 3 Q. Alzheimer's disease of the senile type are
 4 characterized by plaques and tangles?
 5 A. Absolutely right.
 6 Q. Do Downs Syndrome sufferers also develop an Alzheimer's
 7 type dementia?
 8 A. They do.
 9 Q. And is that characterized by plaques and tangles?
 10 A. It is.
 11 Q. And would you describe that as an Alzheimer's type
 12 dementia?
 13 A. It's certainly an Alzheimer's related dementia at
 14 minimum.
 15 Q. What other dementias do you view as being
 16 characterized by plaques and tangles?
 17 A. Of the nature, the amyloid plaques we talked about in
 18 Alzheimer's disease. We know plaques can occur and
 19 tangles can occur in a variety of other conditions, but we
 20 restrict the pathological definition to when there are a
 21 high abundance of both for Alzheimer's disease.
 22 Q. It would be Alzheimer's disease defined as pre-senile
 23 dementia and Alzheimer's type in Downes Syndrome?
 24 A. Correct.
 25 Q. Let me ask you to take a look at the Shaker

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1 A. There are. Still not very well understood.
 2 Q. The muscarinic connection to memory was better
 3 understood than the --
 4 A. Yes. Certainly more prominent. Doesn't mean
 5 nicotinic is important. Muscarinic effects were better
 6 understood earlier.
 7 Q. Is attention a possible effect of nicotinic
 8 stimulation?
 9 A. Certainly. Both muscarinic and nicotinic effects are
 10 involved in attention.
 11 Q. So attention can be the result of nicotinic
 12 stimulation?
 13 A. It can.
 14 Q. Arousal?
 15 A. It can be.
 16 Q. If somebody is looking at galanthamine and seeing
 17 arousal, could be looking at a nicotinic effect?
 18 A. I think arousal is more a muscarinic effect.
 19 Q. Do you know?
 20 A. Pretty sure. Most of the effects of EEG, arousal,
 21 muscarinic effects.
 22 Q. Do you agree that the characteristic hallmark of
 23 Alzheimer's disease pathologically are plaques and tangles?
 24 A. Definitely and synapse loss and neuron loss.
 25 Q. I'm sorry?

1 article.
 2 A. Okay.
 3 Q. Which is DX-483. There's a statement, with regard to
 4 progressive dementia, there appears very little to offer.
 5 Do you see that?
 6 A. I do see that.
 7 Q. And that progressive dementia would include
 8 Alzheimer's disease, in your opinion; is that correct?
 9 A. It would.
 10 Q. What else would it include?
 11 A. It would, for example, include the dementia of
 12 Downs Syndrome that we just talked about I think would
 13 be reasonable. It would include Huntington's Chorea, the
 14 multiple strokes. Lewy body disease, Parkinson's disease.
 15 It would include cortical basal degeneration. Might
 16 include progressive cerebral palsy.
 17 Q. Wernicke-Korsakoff syndrome?
 18 A. We don't view that as a progressive dementia. It
 19 might be viewed on that. I guess depending on the patient,
 20 it could be.
 21 Q. So it would include a great variety of progressive
 22 dementias; is that correct?
 23 A. That's right.
 24 Q. In your opinion, does Shaker describe galanthamine
 25 as a treatment for every one of them?

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1 A. No. He's suggesting I think as a treatment broadly
 2 for the category progressive dementia without going into
 3 etiology.
 4 Q. A person of ordinary skill in the art in 1986 would
 5 read Bhasker as describing galanthamine as a treatment
 6 for all progressive dementias?
 7 A. I think one would read this in 1986 as suggesting
 8 galanthamine for the treatment of proceeding of dementia
 9 as a possible thing to try.
 10 Q. Just so the record is perfectly clear, yes or no?
 11 A. Okay.
 12 Q. Would a person of ordinary skill in the art in 1986
 13 read Bhasker as describing galanthamine as a treatment
 14 for all progressive dementias?
 15 A. I suspect no but it would certainly include
 16 progressive dementias, since there are so many. Since he
 17 doesn't say it, one could conclude.
 18 Q. A person of ordinary skill in the art in 1986 would
 19 not read galanthamine as being described as a treatment
 20 for all progressive dementias. In that case, why would a
 21 person of ordinary skill in the art read it as a treatment
 22 for Alzheimer's disease?
 23 A. I think it's absolutely obvious that Alzheimer's
 24 disease is really the bulk of the causes of progressive
 25 dementia and he's not mentioning specific things, so I

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1 think he's thinking about the specific category of
 2 progressive dementias in suggesting that galanthamine be
 3 used for that.
 4 Q. Does it describe Alzheimer's disease as the most
 5 common dementia?
 6 A. No, but from the eyes in 1986, that is one that
 7 anybody of ordinary skill in the art would understand.
 8 Q. So in forming your opinion on anticipation, did you
 9 include the additional knowledge about Alzheimer's disease
 10 in reaching your conclusion?
 11 A. From the eyes in 1986, I included Alzheimer's disease
 12 as something that one of skill in the arts in 1986 would
 13 include in that umbrella of progressive dementias that
 14 he's was suggesting treatment for, that's correct.
 15 Q. Are you also including the fact that a person of
 16 ordinary skill in the art in 1986 was aware that
 17 Alzheimer's disease was characterized by a deficiency in
 18 acetylcholate function?
 19 A. That's right.
 20 Q. That's not described in the Bhasker article?
 21 A. Right.
 22 Q. The cholinergic deficiency that might link --
 23 something that the person of ordinary skill in the art
 24 would have to bring to the article?
 25 A. That's right. That would be known to somebody

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1 skilled in the art.
 2 Q. They would have known that by reading other
 3 literature; is that correct?
 4 A. That's right.
 5 Q. The, I think the Whitehouse article, the Perry article,
 6 I think the Perry article?
 7 A. That's right.
 8 Q. Would a person of ordinary skill in the art read the
 9 Bhasker describing neostigmine as a treatment for Alzheimer's
 10 disease?
 11 A. He would view it as somebody suggesting cholinesterase
 12 inhibitors. I guess that's right.
 13 Q. But neostigmine does not cross the blood/brain barrier;
 14 correct?
 15 A. That's not correct.
 16 Q. It has very weak central effects?
 17 A. I guess that's right, but somebody skilled in the
 18 art would have read the reference that he's referring to,
 19 Luria, and they did very clear, detailed studies showing
 20 that neostigmine also did and it does, in a brain-
 21 injured patient, cross the blood/brain barrier. So if
 22 you have an injury, it will cross the blood/brain barrier.
 23 What was really important I think for one
 24 skilled in the art, it demonstrated that neostigmine
 25 and galanthamine both could have central properties but

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1 they also have said clearly galanthamine was better than
 2 neostigmine was what was in the literature for central
 3 cognitive problems.
 4 Q. So in reaching your conclusion on anticipation, you
 5 included the knowledge from the Luria article; is that
 6 correct?
 7 A. One doesn't have to, but I knew that is what he was
 8 referring to.
 9 Q. So you, in your opinion, you did include the
 10 knowledge from Luria?
 11 A. Say that again.
 12 Q. In reaching your conclusion, you included the
 13 knowledge from Luria?
 14 A. I included the knowledge he put here in this paper
 15 about Luria's article.
 16 Q. He doesn't cite the article itself?
 17 A. He cited Luria's work.
 18 Q. You, yourself, knew that that was a reference to
 19 the Luria article; correct?
 20 A. And other articles, yes.
 21 Q. So when you reached your conclusion on anticipation,
 22 you included the discussion of galanthamine in the Luria
 23 article?
 24 A. No, that's not true. I think what he says here is
 25 sufficient.

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1 Q. He doesn't distinguish, Bhasker doesn't distinguish
2 in discussing galanthamine between galanthamine and
3 neostigmine?
4 A. That's right.
5 Q. But there's a very important distinction, which is
6 that neostigmine, when the blood/brain barrier is
7 intact, does not have central effects?
8 A. Again, it may not have prominent ones, but it has
9 some.
10 Q. So in your opinion would a person of ordinary skill
11 in the arts in 1986 read Bhasker as describing neostigmine
12 as a treatment for Alzheimer's disease?
13 A. One could have made that interpretation.
14 Q. Is it your opinion that a person of ordinary skill
15 in the art would read the Bhasker article as describing
16 neostigmine as a treatment for Alzheimer's disease?
17 A. Yes, among cholinesterase inhibitors, including
18 galanthamine.
19 Q. Would a person of ordinary skill view that as a
20 reasonable reading?
21 A. I think so.
22 Q. Has neostigmine ever been tried as a treatment
23 for Alzheimer's disease, to your knowledge?
24 A. I strongly doubt it.
25 Q. Why do you strongly doubt it?

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1 A. Because one skilled in the art then also knew that
2 galanthamine was better able to have central effects than
3 neostigmine.
4 Q. So of all the 38 cholinesterase inhibitors that were
5 tried, that didn't include neostigmine; is that correct?
6 A. That's right.
7 Q. Neostigmine would not look like a reasonable
8 candidate?
9 A. Right.
10 Q. It's a peripheral agent?
11 A. It has better peripheral actions because it does not
12 get into the brain as readily.
13 Q. A person of ordinary skill in the art in 1986 is
14 going to recognize neostigmine is not reasonably
15 construed for being a treatment for Alzheimer's?
16 A. Correct.
17 Q. If we read Bhasker as talking about things like head
18 injury and local brain damage, that is as you mention from
19 your reading of the Luria article, neostigmine then could
20 have central effects?
21 A. It could. Even when it's not damaged. I guess what
22 he's referring to here is using this for de/inhibition.
23 That's really what he says precisely and neostigmine
24 did have that property of de/inhibition.
25 Q. That was sort of the restarting of temporarily arrested

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1 neurons?
2 A. Right.
3 Q. Not dead neurons. Temporarily arrested neurons?
4 A. That's right.
5 Q. That's not Alzheimer's disease; is that correct?
6 A. Nothing -- nothing improves function of dead neurons.
7 That's right. Even in Alzheimer's disease. We're using
8 these drugs for the same manner. To restore function of
9 injured neurons.
10 Q. So this de/inhibition, that's not directly applicable
11 to Alzheimer's disease because Alzheimer's disease is --
12 A. It is applicable. We're talking about dead neurons
13 containing acetylcholine.
14 Q. What Luria described was temporarily arrested neurons;
15 is that correct?
16 A. That's right.
17 Q. And temporarily arrested neurons does not describe
18 Alzheimer's disease?
19 A. He also described them as permanent. Really what he
20 was saying, he coupled the inhibition with education of
21 the brain because they would be permanently silent unless
22 you educated the brain while they were temporarily
23 inactive.
24 Q. This idea of temporarily inactive, that's not
25 applicable to Alzheimer's?

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1 A. That is right.
2 Q. You mentioned a number of other functional deficits. I
3 think one was praxic function, a decline in praxic function?
4 A. That's right.
5 Q. That's not memory?
6 A. Sort of a type of memory. Motor memory. Memory for
7 skilled movements.
8 Q. It's not the amnesia that was the signature feature
9 in Alzheimer's disease?
10 A. That's correct.
11 Q. Gnostic function, that's not amnesia either?
12 A. It's a special type of perceptual amnesia.
13 Q. Agnosia is distinguished from amnesia?
14 A. Yes.
15 Q. So gnostic function is seen as a different function?
16 A. Yes.
17 Q. Aphasic symptom, that's different, too?
18 A. That's right.
19 Q. That's speech?
20 A. That's right. It's language.
21 Q. Let me ask you a few questions about the patent, if
22 I could, because I confess to be a little confused about
23 your caveat with regard to your enablement opinion.
24 Do you believe, is it your opinion that a
25 person of ordinary skill in the art in 1986, reading the

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1 '318 patent, and bringing to bear whatever else he or
2 she would know from reading the literature, would he or
3 she believe that there was a method of treating
4 Alzheimer's disease and related dementias by administering
5 to a patient suffering from such a disease a therapeutically
6 effective amount of galanthamine?
7 A. What was the caveat?
8 Q. A person of ordinary skill in the art in 1986 reading
9 the patent and the available literature, would he or she
10 believe that galanthamine would be a treatment for
11 Alzheimer's disease?
12 A. Using the available literature, the prior art, assuming
13 obviousness was not thrown out?
14 Q. Without assuming anything, you wanted to know your
15 opinion based on the knowledge of the literature.
16 A. Yes.
17 Q. A person in 1986 reading the patent would believe
18 that galanthamine would be a treatment for Alzheimer's
19 disease; is that correct?
20 A. That's right.
21
22 Q. And such a person would be able to use galanthamine as
23 a treatment-- could find therapy in an effective dose;
24 correct?
25 A. Yes, treatment by improving symptoms as was stated in

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1 the patent as the goal.
2 Q. Improving cognitive symptoms; correct?
3 A. Correct.
4
5 Q. Did you testify at your deposition that the proof of
6 concept for galanthamine in Alzheimer's disease occurred
7 after the patent?
8 A. I don't remember that sitting here.
9 Q. Perhaps we can refresh your recollection.
10 A. Okay.
11 A. I still believe it.
12 Q. You agreed that the proof of concept for galanthamine
13 as a treatment for Alzheimer's disease occurred after 1986;
14 is that correct?
15 A. I think the proof of concept included lots of things,
16 but I think the highest bar, most definitive evidence came
17 afterward, that's right, meaning the human studies came
18 later.
19 Q. Let me see if I can just make that as clear as
20 possible. Let me just hand you a copy just to refresh
21 your recollection.
22 A. Okay.
23 MR. SIPES: If I my approach...
24 THE COURT: Yes.
25 (Mr. Sipes handed an exhibit to the witness.)

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1 BY MR. SIPES:
2 Q. If you will turn to Page 240 of your deposition,
3 beginning at Line 8, you'll recall I asked you, and was
4 there proof of concept for galanthamine in humans before
5 January of 1986?
6 Answer: Not proof of concept in Alzheimer's
7 disease.
8 When did proof of concept for galanthamine in
9 treating Alzheimer's disease first arise, in your opinion?
10 Answer: I don't know. After the patent.
11 Do you see that?
12 A. Yes.
13 Q. Does that refresh your recollection that that was
14 your testimony at the deposition?
15 A. That's right. I think I heard your question earlier
16 a little bit different. Here, this was defined for proof
17 of concept for galanthamine in humans. So for humans,
18 certainly, the proof of concept came later.
19 Q. So proof of concept for treating humans with
20 Alzheimer's disease with galanthamine was after the
21 patent?
22 A. That's right.
23 Q. And did you think that the idea of using
24 galanthamine as a treatments for Alzheimer's disease in
25 1986, was that scientifically reasonable judgment?

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1 A. Definitely.
2 Q. Now, I believe your counsel asked you to consider
3 the factor of whether a person of ordinary skill would
4 believe without question that galanthamine would be a
5 treatment for Alzheimer's disease.
6 Do you recall that?
7 A. I do.
8 Q. Now, Alzheimer's disease is a tricky disease;
9 correct?
10 A. It is.
11 Q. In your opinion, what kinds of tests would be required
12 before a person of ordinary skill in the art would believe,
13 without question, that a drug would work as a treatment for
14 Alzheimer's disease?
15 A. I think the answer to that is that you really need to
16 see very strong evidence that it works, meaning you need to
17 see trials in humans, multi-center, perhaps clinical trials
18 of patients that are designed with appropriate experimental
19 methods so that you can know the chance of positive or
20 negative results are fairly low, occurring by chance,
21 being negative or positive.
22 So that's the kinds of evidence I would say
23 that one would really need to accept without question.
24 Q. So that would be phase three trials?
25 A. It could be. I think it might depend on the phase

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1 two.
 2 Q. Large clinical trials. Phase two or phase three?
 3 A. That's right.
 4 Q. So to meet the enablement standard your counsel
 5 posed to you, you would really want to see phase two or
 6 phase three trials with galanthamine; is that correct?
 7 A. That's right.
 8 Q. Do you think Dr. Bonnie Davis could have afforded
 9 phase two or phase three trials with galanthamine?
 10 A. Sure. Not by herself. Maybe she's more wealthy
 11 than I realize.
 12 Q. Is it the standard in the field where you practice
 13 to wait to file patent applications until after phase two
 14 or phase three trials are under way?
 15 A. Absolutely not.
 16 Q. Is that contrary to pretty much every drug company
 17 which has attempted to find a treatment for Alzheimer's
 18 disease?
 19 A. It is.
 20 MR. SIPES: Your Honor, if I may have a moment
 21 just to confer with some wiser colleagues...
 22 (Pause while counsel conferred.)
 23 MR. SIPES: Your Honor, with permission to
 24 approach, please?
 25 (Mr. Sipes handed an exhibit to the witness.)

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1 BY MR. SIPES:
 2 Q. Dr. Levey, I've handed you a copy of Plaintiffs'
 3 Exhibit 756, a document entitled Galanthamine: Another
 4 Look at an Old Cholinesterase Inhibitor, by Edward F.
 5 Domino that was published in 1988, two years after the
 6 patent was filed.
 7 Do you see that?
 8 A. I do.
 9 Q. This was an article, in fact, you cited in your --
 10 your expert report as providing a good summary of
 11 galanthamine; is that correct?
 12 A. That's correct.
 13 Q. And I think you may have referred to Dr. Domino as
 14 a world famous pharmacologist; is that correct?
 15 A. He is, yes. I did refer to him that way.
 16 Q. And he's, in fact, in the courtroom. He's one of
 17 the defendants' experts; is that correct?
 18 A. That's right.
 19 Q. Now, you've testified in your opening that one of
 20 the things that would have led a person of ordinary skill
 21 in the art to galanthamine from physostigmine was its
 22 longer duration of action; is that correct?
 23 A. That's correct.
 24 Q. And one of the articles I think you cited was a
 25 Baraka; correct?

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1 A. That's right.
 2 Q. If you will turn to the second -- the third page of
 3 Dr. Domino's survey of galanthamine, you'll see a discussion
 4 of the Baraka article.
 5 Do you see that?
 6 A. I do.
 7 Q. That's the same article you were discussing; is that
 8 correct?
 9 A. That's right. It is.
 10 Q. Let's take a look at the last sentence of the
 11 discussion.
 12 MR. SIPES: If you can pull up the whole
 13 paragraph...
 14 BY MR. SIPES:
 15 Q. Dr. Domino concludes after his study of the Baraka
 16 article in 1988 that, although the authors concluded that
 17 galanthamine produced a long-lasting reversal of the
 18 anti-cholinergic syndrome, from the study, one could
 19 determine that the drug lasted two hours.
 20 A. I see that.
 21 Q. Two hours was the duration of action of oral
 22 physostigmine in the '85 paper; is that correct?
 23 A. That's correct.
 24 Q. And, in fact, now, if you will turn to Dr. Domino's
 25 conclusions under the summary, Page 301...

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1 A. Okay.
 2 Q. You'll see that there's a summary?
 3 A. I do.
 4 Q. He describes galanthamine as less potent than
 5 physostigmine and with a similar duration of action.
 6 Do you see that?
 7 A. I see that.
 8 Q. That was Dr. Domino's conclusion at least in the
 9 published literature from his review of galanthamine?
 10 A. I see that.
 11 Q. That it was both less potent and had a similar
 12 duration of action; correct?
 13 A. I see that.
 14 Q. Would that appear to be promising, the fact that it
 15 was less potent and no longer-acting?
 16 A. If you took that by itself, I would say no, but
 17 obviously there's other evidence and other interpretations.
 18 Q. But at least from the world renowned Dr. Domino,
 19 that was his conclusion in 1988; is that correct?
 20 A. That's what he wrote. That's right.
 21 MR. SIPES: If you will bear with me...
 22 (Pause.)
 23 BY MR. SIPES:
 24 Q. All right. Let me...
 25 (Pause.)

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1 MR. SIPES: If I may approach the witness, your
 2 Honor...
 3 THE COURT: Yes, you may.
 4 (Mr. Sipes handed an exhibit to the witness.)
 5 MR. SIPES: Before I do that, I can't recall
 6 if I moved Plaintiffs' Exhibit 756 into evidence, but I
 7 will do so now.
 8 THE COURT: Any objection?
 9 MR. LOMBARDI: Domino?
 10 MR. SIPES: Domino.
 11 MR. LOMBARDI: No objection.
 12 THE COURT: Thank you.
 13 DEPUTY CLERK: So marked.
 14 *** (Plaintiffs' Exhibit No. 756 was received into
 15 evidence.)
 16 BY MR. SIPES:
 17 Q. Dr. Levey, I've handed you Plaintiffs' Exhibit 1228,
 18 which is an article by Alan I. Levey, entitled, Muscarinic
 19 Acetylcholine Expression in Memory Circuits: Implications
 20 for Treatment of Alzheimer's Disease.
 21 Do you see that?
 22 A. Yes.
 23 Q. This is from the proceedings of the National Academy
 24 of Sciences in 1996, was it not?
 25 A. It is.

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1 Q. That's a very prestigious journal?
 2 A. Prestigious journal.
 3 Q. You tried to be truthful and accurate in this
 4 paper, did you not?
 5 A. I was.
 6 Q. And you considered the article very important; is
 7 that correct?
 8 A. That's right.
 9 MR. SIPES: Let me move into evidence Plaintiffs'
 10 Exhibit 1228, if I may.
 11 MR. LOMBARDI: No objection.
 12 THE COURT: Thank you.
 13 DEPUTY CLERK: So marked.
 14 *** (Plaintiffs' Exhibit No. 1228 was received into
 15 evidence.)
 16 BY MR. SIPES:
 17 Q. First, let me ask you to look on the first page of
 18 Plaintiffs' Exhibit 1228, in the right-hand column.
 19 If you look at the sentence, sort of halfway
 20 through the first full paragraph... Further down than that.
 21 There's a discussion of tacrine. Do you see
 22 that? Tacrine yields dose-related significant
 23 improvements in several mechanisms and quality of life
 24 substantiating a cholinergic role in the pathophysiology
 25 of the disease. That's what you are writing in 1996;

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1 correct?
 2 A. That's right.
 3 Q. Ten years after Dr. Davis' patent; is that right?
 4 A. That's right.
 5 Q. But then you say, yet the overall clinical benefits
 6 of this drug are disappointing and may be related to its
 7 indirect mechanism of action, which depends on the
 8 synthesis, storage and release of acetylcholine by
 9 surviving cholinergic neurons. In addition, side effects
 10 resulting from the nonspecific activation of cholinary
 11 are -- do you see that?
 12 A. I do.
 13 Q. That concern with the pre-synaptic neuron, those are
 14 the same concerns that were expressed back in 1985; is that
 15 correct?
 16 A. That's right.
 17 Q. But even in 1996, you continued to believe that
 18 cholinesterase inhibitors were hampered by that; is that
 19 correct?
 20 A. That's right. We had no evidence that any drugs
 21 were better yet than the positive effects that we're
 22 seeing early on.
 23 Q. And so you were --
 24 A. It's modest.
 25 Q. -- continue to pursue muscarinic agonists?

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1 A. That's right.
 2 Q. And if you will turn to the last page under your
 3 conclusions, you'll see -- two pages back. Right under
 4 Conclusions, just pull up that whole paragraph under
 5 Conclusions.
 6 It says, Presently used, cholinergic compounds
 7 suffer from a lack of subtype selectivity and potency,
 8 which favor negative peripheral side effects and may
 9 limit cognitive effects because of weak and/or opposing
 10 actions in brain.
 11 Do you see that?
 12 A. I do.
 13 Q. Now, the presently used cholinergic compounds that
 14 you are talking about there are cholinesterase inhibitors
 15 among other things?
 16 A. Yes. I think I was referring to the receptors by
 17 that statement, really. That the receptors -- receptor
 18 agonists available were non-selective.
 19 Q. Well, are cholinesterase inhibitors cholinergic
 20 agents as well?
 21 A. Yes.
 22 Q. Do they suffer from a lack of subtype selectivity in
 23 potency?
 24 A. Yes, they are. Just as I'm reading this, I'm
 25 thinking this paper was about muscarinic receptors. I

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1 think we're talking about agonists primarily, or that's
2 what I had in mind when writing it. Absolutely right.
3 It includes cholinesterase inhibitors.

4 Q. Did you believe in 1996 that both cholinesterase
5 inhibitors and the then available muscarinic agonists
6 selected from the subtype selectivity and potency?

7 A. Absolutely. I don't know about potency, but
8 certainly there wasn't -- that one couldn't achieve as
9 high levels in the brain as one might want because of the
10 peripheral side effects.

11 Q. So that would be a problem with potency, would it
12 not?

13 A. Not necessarily. It's more selectivity.

14 Q. And as we've seen, galanthamine is even less potent
15 than physostigmine?

16 A. Yes.

17 Q. Galanthamine is no more selective than physostigmine;
18 is that correct?

19 A. Say that again.

20 Q. Galanthamine is not selective for the muscarinic
21 receptor, correct?

22 A. That's right.

23 Q. In fact, what we've seen is it appears to have weak
24 muscarinic effects?

25 A. In some conditions and strong in others, yes.

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1 right?

2 A. That's right.

3 Q. And you said something about everybody jumping on

4 the bandwagon?

5 A. I did.

6 Q. What did you mean by that?

7 A. Well, what I meant is, I think of the -- as was

8 mentioned, it cost companies sometimes \$500 million or

9 more to bring these drugs to clinical trial. One doesn't

10 make that kind of investment without a very good --

11 without a strong belief that it's likely to be successful.

12 I mean, drugs get whittled down to one or two that can

13 actually get tested by a company.

14 So the fact that there are 38 in trial means

15 lots of people were making lots of big investments because

16 they believed that already there had been strong proof of

17 principle that cholinesterase inhibitors could be effective

18 treatments in terms of efficacy. That had been

19 demonstrated, I believe, and that's why all these companies

20 invested hundreds of millions of dollars, just the numbers

21 of investigators and companies doing it I think says that

22 very clearly, because everybody realized what you really

23 needed is to overcome the safety issues, the side effect

24 issues. If you could get safer, better tolerated drugs,

25 then not only would it be an effective treatment, but it

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1 also would beat out other drugs and be more likely to be

2 approved by the FDA.

3 Q. Okay. Now, when counsel asked you questions about

4 those drugs, did he provide you with any information

5 about the state of the art relative to those drugs prior

6 to the time people started to work with them as

7 cholinesterase inhibitors?

8 A. No.

9 Q. And we know something about the state of the art of

10 galanthamine prior to the time it was selected as a

11 treatment for Alzheimer's disease, isn't that right?

12 A. We know a lot about it. That's right.

13 Q. And what was the state of the art with respect to

14 galanthamine at that time?

15 A. Well, as we have gone through, we knew that it had

16 been used in humans. We knew that it had been used in

17 humans with cognitive deficits. We knew that it had been

18 able to, some of the cognitive deficits and local brain

19 injury or arrestable dementias, whatever one wants to call

20 the underlying cause, that galanthamine was able to be

21 effective in some of the symptoms most responsible were

22 the cognitive ones, according to the literature.

23 So we knew that it was safe, well tolerated,

24 able to get into the brain. It had relatively long

25 duration of action. Whatever one wants to conclude the

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EXHIBIT 2

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1 at Page 688, please, Doctor?
2 Does this indicate what some of the limitations
3 were with physostigmine?
4 A. Yes.
5 Q. Okay. Could you describe that for the Court?
6 A. Well, basically, it says that it's a compound that
7 is short-acting. We know that. Less than an hour,
8 depending on the administration and, in addition, it
9 has a number of peripheral effects, which are
10 objectionable.
11 Q. In your opinion, Dr. Domino, what would this article
12 have taught a person of skill in the art as of 1986?
13 A. To go full speed ahead to find another member in
14 the family of reversible cholinesterase inhibitors that
15 penetrate the blood/brain barrier.
16 Q. As a factual matter, what did happen with respect
17 to research in cholinesterase inhibitors?
18 A. Well, the field started to explode and a great deal
19 of work was being subsequently developed. And that's why
20 we have what we have today.
21 Q. Doctor, you just indicated that this article would
22 teach a person of skill to move full speed ahead with
23 looking at other reversible cholinesterase inhibitors.
24 The qualifications or the characteristics you
25 just described, does that encompass any particular drug?

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1 A. Yes.

2 Q. What does the prior art tell you?

3 A. Well, the prior art tells you that galanthamine is
4 a -- is a method to then treat, as stated in Claim 1,
5 with the dosages to be given orally. That is known. And
6 a dose range 10 to 2,000. Well, the low dose certainly
7 was known.

8 Q. And in 1986, would a person of skill in the art have
9 been motivated to combine, I think you relied on the
10 Rathmann and the Daskalov references. Would a person of
11 skill in the art have been motivated to combine those?

12 A. Absolutely.

13 Q. Why?

14 A. That makes sense. It's your fundamental knowledge,
15 your base of what's going on in the art.

16 Q. And would a person of skill in the art have had a
17 reasonable expectation of success in '86 that
18 galanthamine could be used orally in dosage amounts
19 disclosed in the patent?

20 A. Yes.

21 Q. So based on your review of the prior art, Dr.
22 Domino, what is your opinion with respect to Claim 4 as
23 to whether it's obvious?

24 A. Well, I think Claim 4 is obvious on the low dose
25 side.

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1 Q. Can you identify it, please?
2 A. Yes. This is my article called galanthamine:
3 Another look at an old cholinesterase inhibitor.
4 Q. When did you publish this article?
5 A. This was published in book form in I believe '88.
6 Q. When did you begin thinking of writing about this?
7 A. Well, I know -- I don't remember exactly, but I
8 know that there was a meeting in March of that year and
9 I was invited by Professor Giacobini to present
10 something on choline -- something in my area of
11 expertise and so I must have started doing a literature
12 search to write the article earlier, maybe in '87. I
13 don't remember.
14 Q. And you said you were invited to a meeting. What
15 meeting were you invited to?
16 A. Well, this was a meeting to trying to summarize
17 the whole field of cholinesterase inhibitors and their
18 role in, as potential therapies, symptomatic therapies
19 for Alzheimer's disease.
20 Q. Now, at the time that you wrote your article, did
21 you know if Dr. Davis had a patent on galanthamine for
22 Alzheimer's disease?
23 A. I had no idea whatsoever.
24 Q. And when is the first time you learned she had a
25 patent?

1 we're talking about a dose. And, therefore, you get a
2 dose effect curve. So potency refers to the dose.
3 Q. Okay. And as a factual matter, is galanthamine less
4 potent than physostigmine?
5 A. Absolutely.
6 Q. All right. How much less potent?
7 A. About -- from the data in the literature that I have
8 reviewed, it's in the order of about a tenth of the potency
9 of -- of physostigmine.
10 Q. So what was -- what were the doses of physostigmine
11 that were being administered up to 1986?
12 A. Well, you are talking about oral administration as
13 an example. They're generally in the order of .5l,
14 something two, something in that range. Particularly the
15 Davises, Ken Davis and in particular his colleagues have
16 done a lot of work in that. Maybe Bonnie was involved.
17 I don't remember.
18 Q. So what would the equivalent dose have been for
19 galanthamine?
20 A. Well, easy. Multiply it by ten.
21 Q. Okay. Now, does the fact that galanthamine is
22 less potent than physostigmine mean that it would be
23 less effective as a cholinesterase inhibitor?
24 A. Not at all. That's a crucial point.
25 Q. Why is that crucial?

1 Q. Is that -- would that have been consistent with a
 2 person of skill in the arts view in 1986?
 3 A. Yes.
 4 Q. Now, Dr. Domino, I want to talk about the next
 5 skeptical comment, which is that, because the precursor
 6 route to treating Alzheimer's disease did not show
 7 improvement, at least as of 1986, that that would have
 8 discouraged people from pursuing cholinesterase inhibitors.
 9 Do you recall that comments?
 10 A. Yes, I do recall the comment, yes, I do.
 11 Q. Okay. And do you agree with it?
 12 A. No, I do not.
 13 Q. Why not?
 14 A. Because the -- there never was in human beings
 15 evidence that the precursor route was, indeed, effective
 16 in improving memory or whatever in human beings. I
 17 actually lost a year of my life doing work not with
 18 Alzheimer's patients, but with normal aged individuals,
 19 giving them loads of the precursor lecithin, which is --
 20 that's what makes ice cream smooth when you taste it and
 21 swallow it. All I managed to do was get them fat. Too
 22 much ice cream and phosphotitocholine with no effect and
 23 subsequently, additional work that was done by me, but
 24 also by others, using then phosphotitocholine actually
 25 in Alzheimer's patients. Again, showed that it

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1 fundamentally was not effective, which caused me to
 2 repeat some of the original work reported in the -- and I
 3 did it.
 4 There were others that did it in rats that
 5 disagreed with Rathmann. I was unfamiliar with that work
 6 at that time. I did it in mice. It showed there was no
 7 effect.
 8 So I think it was a wonderful, wonderful idea
 9 that had no basis in fact.
 10 Q. And did the fact that based on your experience,
 11 the precursor route didn't work, did that deter you or
 12 deter others from looking at cholinesterase inhibitors?
 13 A. Not at all.
 14 Q. What effect did it have?
 15 A. Well, the effect was you've got to go into other
 16 routes or otherwise ways of affecting acetylcholine or
 17 acetylcholine function.
 18 Q. And what time period were you doing the work on the
 19 precursor route?
 20 A. I was doing the work at the time that Dr. Gershon,
 21 a very well-known psychopharmacologist, was Director at
 22 the clinic. My recollection is he came in around 19 --
 23 I'm sorry -- 1979, something like that. And I worked
 24 with his group until '83, when I then left the Lafayette
 25 Clinic.

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1 Q. Now, did you also have experience in the agonist
 2 approach at the Lafayette Clinic?
 3 A. The answer is yes.
 4 Specifically with arecoline.
 5 Q. Plaintiffs' experts indicated that because the
 6 agonist approach looked more promising it, would have
 7 caused skepticism for the cholinesterase inhibitor
 8 approach?
 9 A. I don't think it would cause any skepticism. Was
 10 just another way of approaching things. There was some
 11 studies with arecoline that were positive. Some were
 12 negative. We thought our study, I thought, did very
 13 well, was negative.
 14 I don't think it would deter anyone from
 15 pursuing other ways of enhancing acetylcholine in the
 16 brain.
 17 Q. And as a factual matter, did it deter others from
 18 pursuing cholinesterase inhibitors?
 19 A. Not at all.
 20 Q. What evidence do you have of that?
 21 A. The best evidence is reading that Giacobini table
 22 that he published about all of the cholinesterase
 23 inhibitors that a large variety of drug companies were
 24 developing and had in human clinical trials.
 25 Q. We'll look at that in a minute.

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1 A. Well, the field exploded with many other compounds
2 being tested by many pharmaceutical companies.
3 Q. How do you control peripheral side effects? What
4 can you do to control those?
5 A. Well, the easiest way of controlling side effects is
6 via a good dose.
7 Q. Was that known in 1986?
8 A. It's known then and now.
9 Q. And I want to go to the next category of secondary
10 considerations plaintiffs' experts identified.
11 Would you identify this for the Court, please?
12 A. Yes. This is a -- the plaintiffs' experts opinion
13 on failure of others.
14 Q. Okay. And what do you understand those to be
15 referring to when they say failure of others?
16 A. Well, that there were many other, or other people
17 that were involved in the field that used a variety of
18 drugs or -- including cholinergic treatments that
19 apparently failed.
20 Q. Okay.
21 A. Or did fail.
22 Q. And did plaintiffs yesterday in opening statement
23 put up a slide that they showed a timeline indicating
24 various treatment approaches, both before and after Dr.
25 Davis' patent?

1
2 A. There were different forms. As I remember, I'd have
3 to look it up.
4 Q. But you do recall it was either oral or parental?
5 A. Yes, but trouble. Pulse, relax, wait.
6 Q. And by parental, that's injection; correct?
7 A. I believe so. I'd have to watch it. I don't
8 know. I'd have to review that schistosomiasis literature.
9 Q. But the point is it was used sort of in acute
10 fashion rather than chronically?
11 A. It's a very important point.
12 Q. It's very important to the question of tolerability
13 of side effects; is that correct?
14 A. That is correct.
15 Q. And something that is used acutely may not be safe
16 or tolerable when used chronically; is that correct?
17 A. Depends on the dose.
18 Q. The amount of drug given?
19 A. That is correct.
20 Q. But also if it turns out as it did with Metrifonate
21 that a drug that appeared safe and tolerable when used
22 acutely was not safe and tolerable for using it
23 chronically in treating Alzheimer's disease; is that
24 correct?
25 A. That is correct, because it produced the same

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1 effects as a nerve agent.
2 Q. And of course to treat Alzheimer's disease,
3 you're looking for a chronic treatment; is that correct?
4 A. That is correct.
5 Q. Now, you say that some reason to control side
6 effects by dose. The idea is if you lower the dose,
7 you'll have fewer side effects; is that correct?
8 A. Yes.
9 Q. That's how you control dose. You use less of the
10 drug?
11 A. Yes.
12 Q. Let me talk to you a little bit about your view of
13 physostigmine.
14 Now, before 1986, physostigmine was used
15 therapeutically; is that correct?
16 A. Yes.
17 Q. And, in fact, it continues to be used
18 therapeutically under the trade name antilirum (phonetic);
19 correct?
20 A. Yes.
21 Q. That's quite an old trade name. That goes way back
22 before 1986?
23 A. Yes.
24 Q. One way it can tell, it almost suggests its use,
25 which FDA doesn't let you do any more?

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1 A. Yes.
2 Q. The use of antilirum is to reverse the delirium by
3 things such as scopolamine?
4 A. Yes.
5 Q. That's an acute use?
6 A. Yes.
7 Q. Physostigmine was safe and tolerable in that use?
8 A. Yes.
9 A. Yes.
10 Q. But you agree physostigmine was not safe and
11 tolerable for using in treating Alzheimer's disease; is
12 that correct?
13 A. That is correct.
14 Q. In fact, you have admitted that physostigmine was
15 recognized in the art as a failure by 1986; is that
16 correct?
17 A. From the point of view of a therapeutic agent for
18 the symptomatic treatment of Alzheimer's patients.
19 Q. And, in fact, it's your opinion that it was well
20 known prior to 1986 that physostigmine had too many
21 peripheral side effects to be used as a treatment for
22 Alzheimer's disease; correct?
23 A. It was shown by the Davis' and their extensive
24 excellent work that, indeed, physostigmine had a number
25 of side effects, but it was therapeutically effective.

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1 This is an important point, which establishes proof of
2 concept in human beings, that a cholinesterase inhibitor
3 works.
4 Q. But it -- you say it was shown to have effect, but
5 it was also known to have too many peripheral side effects
6 to be used for the treatment of Alzheimer's disease;
7 correct?
8 A. As used from a clinical point of view.
9 therapeutically, with chronic therapy, but it's crucial
10 that it was an important agent that showed proof of
11 concept.
12 Q. And the peripheral side effects of physostigmine
13 that prevented its clinical use in treating Alzheimer's
14 disease were what you called the slud syndrome;
15 correct?
16 A. Salvation, lacrimation, diarrhea, you can add
17 vomiting and a number of other things, ultimately ending
18 up in convulsions.
19 Q. These were all peripheral cholinergic side effects;
20 is that correct?
21 A. The first were, not the last.
22 Q. I don't understand.
23 A. If you have a seizure, it's essential.
24 Q. So the seizure was central, but that's bad; correct?
25 But the rest of them were cholinergic side

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1 effects?

2 A. That is correct.

3 Q. Physostigmine was perceived to have too many

4 cholinergic side effects to be used clinically to treat

5 Alzheimer's disease?

6 A. Yes.

7 Q. You testified if Forest Laboratories had come to

8 you in 1986 and asked whether they should develop

9 physostigmine as a drug product that became known as

10 physostigmine SR, you would have told them no. Waste

11 of time; correct?

12 A. Correct, because of the side effects. They are

13 hoping that there would be tolerance to the side effects,

14 but that the therapeutic effects would last. I don't know

15 of any such evidence. Maybe there is, but I was -- I am

16 unaware of it.

17 Q. But unfortunately, Forest never went to you because,

18 in fact, they did try to develop physostigmine SR as a

19 commercial drug product; correct?

20 A. They did.

21 Q. And that did fail; is that correct?

22 A. It failed for clinical, for FDA reasons that it

23 failed, so that's why I think there has to be a very clear

24 distinction in everybody's mind and especially our Judge

25 on the difference between efficacy, a beneficial effect

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1 versus a failure from a commercial point of view for FDA

2 approval. Unless that is made perfectly clear, then

3 we're not communicating at all.

4 Q. And just so that we're clear, it was recognized in

5 the art that one of the problems with developing a

6 treatment for Alzheimer's disease that could be used

7 clinically was the problem with side effects; correct?

8 A. That is correct.

9 Q. So people knew in the art in 1986 that one of the

10 problems they would have to overcome to develop a

11 treatment for Alzheimer's disease that could be used

12 clinically would be to overcome problems with safety

13 and tolerability; correct?

14 A. That is correct.

15 Q. Let me try to look at some of the things that you

16 were doing in the early eighties.

17 MR. SIPES: May I approach the witness?

18 THE COURT: Yes, you may.

19 (Mr. Sipes handed an exhibit to the witness.)

20 BY MR. SIPES:

21 Q. Dr. Domino, I've handed you an exhibit that has

22 been marked as DX-557. It is an article by Munzio Pamera

23 (phonetic), Robert Block, Joy Abraham, Edward F. Domino

24 and Samuel Gershon entitled Combined Precursor Treatment

25 and dihydroergotoxaminemesillate (phonetic) in Alzheimer's

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1 disease.

2 Do you see that?

3 A. Yes.

4 Q. This is an article that you published with some

5 colleagues at the Lafayette Clinic in 1983; is that

6 correct?

7 A. Yes. I'm proud of it.

8 MR. SIPES: I will move the admission of

9 DX-557.

10 MS. ULRICH: No objection.

11 THE COURT: Thank you.

12 DEPUTY CLERK: So marked.

13 *** (Defendants' Exhibit No. 557 was received into

14 evidence.)

15 BY MR. SIPES:

16 Q. Dr. Domino, you published this as indicated in 1983;

17 correct?

18 A. That is correct.

19 Q. And this reports on work that you did with colleagues

20 on patients in the Lafayette Clinic?

21 A. That is correct.

22 Q. And the patients were patients with Alzheimer's

23 disease?

24 A. That is correct.

25 Q. And let's me ask you to read the first sentence.

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1 Let's pull up the first paragraph, if you could, Matt.

2 It reads, The consistent and selective

3 reductions in the brain activity of

4 cholinacetyltransferase, the biosynthetic enzyme for

5 acetylcholine, have led to numerous attempts at enhancing

6 central cholinergic activity in individuals with

7 Alzheimer's disease by means of cholinergic precursors in

8 the hope of ameliorating the cognitive dysfunction.

9 Do you see that?

10 A. Yes.

11 Q. That's referenced as the precursor to treat

12 Alzheimer's disease?

13 A. Yes.

14 Q. That's based on the cholinergic deficit hypothesis?

15 A. Yes.

16 Q. The outcome of these therapeutic strategies which

17 have utilized cholinergic precursors alone has been

18 generally disappointing.

19 Do you see that?

20 A. Yes.

21 Q. That was true in your mind?

22 A. Yes.

23 Q. You then say, there is, however, a preliminary

24 report from an open trial suggesting increased efficacy

25 from the combination of choline and piracetam, a

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1 pharmacologic agent which is thought to improve neuronal
2 metabolism.

3 Do you see that?

4 A. Yes.

5 Q. You were describing a different way of addressing
6 the cholinergic deficit hypothesis in 1983?

7 A. Yes.

8 Q. That's using the agent peracetin combined with a
9 precursor?

10 A. Yes.

11 Q. Piracetam was under the category as you previously
12 described a metabolic enhancer?

13 A. I don't know if I said that word, but that's what
14 it is thought to be.

15 Q. I think you were with counsel looking at a chart
16 as what you were describing as failures and one category
17 was metabolic enhancers. Do you recall that?

18 A. Yes.

19 Q. And one sub-category of metabolic enhancers were
20 the nootropes?

21 A. Nootropic agents.

22 Q. Nootropic --

23 A. That's the wrong way to pronounce it.

24 Q. The nootropic agents were newly-developed agents
25 thought to boost brain metabolism; is that correct?

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1 A. That's correct.

2 Q. And they were being used in combination with choline
3 in an effort to address the cholinergic deficit; is that
4 correct?

5 A. Yes.

6 Q. So this was yet another strategy to try to address
7 the cholinergic deficit hypothesis; is that correct?

8 A. Yes.

9 Q. And, in fact, as of 1983, there was a suggestion
10 of increased efficacy based on an open trial in humans;
11 is that correct?

12 A. That is what it says.

13 Q. So that would have been under your lights and
14 encouraging report on piracetam; correct?

15 A. That's why we did what we did.

16 Q. And you studied a different metabolic enhancer;
17 correct?

18 A. Yes.

19 Q. You studied dihydroergotoxaminemesilate (phonetic);
20 is that correct?

21 A. Yes. Hydergine.

22 Q. The trade name is Hydergine?

23 A. That is correct.

24 Q. And I think both, to spare both of us and the Court
25 Reporter, why don't we refer to it as Hydergine (phonetic),

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1 its trade name. Would that be all right?

2 A. Sure.

3 Q. So you did a study of a precursor with Hydergine to
4 try to treat Alzheimer's disease; correct?

5 A. Yes.

6 Q. You did that at the Lafayette Clinic with Sam
7 Gershon and others?

8 A. Yes.

9 Q. So at the time, this was thought to be a promising
10 approach to treating Alzheimer's disease; is that
11 correct?

12 A. It was one of the approaches, yes.

13 Q. You don't give drugs to patients you don't think
14 are going to work, do you?

15 A. I thought it was worthwhile to try.

16 Q. And if you will turn to the conclusions, your
17 conclusion at the end of this -- first, you say, both
18 drug treatments led to some subjective improvement
19 without any consistent improvements on objective
20 psychometric measures as has been previously reported
21 with Hydergine treatment.

22 A. Yes.

23 Q. Both treatments you are saying are with Hydergine
24 with or without precursor?

25 A. Yes.

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1 Q. You were seeing subjective improvements?

2 A. Yes.

3 Q. That would be an overall impression of the
4 functionality of the patient; is that correct?

5 A. Yes. There were some subjective improvements.

6 Q. That's the same sort of subjective evaluation that
7 for example Dr. Summers was doing with tacrine at the
8 time in his open label tacrine study at the time?

9 A. Wait a minute. What study are you referring to?

10 Q. His 1981 study.

11 A. Could you show me that article? I'd be glad to
12 review it and comment on it.

13 Q. You don't recall sitting here today whether that was
14 an open or closed trial?

15 A. I remember that -- I don't remember the details of
16 that trial. I want to compare it to what you're asking
17 me to compare to what we did with our study.

18 Q. That's all right. I will just ask you about your
19 study, then. That's fine.

20 So you were reporting subjective improvements
21 in the functioning of patients with Hydergine; is that
22 correct?

23 A. That says what it says.

24 Q. And at this time you don't write in your '83
25 paper suggesting cholinesterase as an alternative, do you?

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1 A. Apparently I don't, yes.
2 Q. You certainly never mentioned galanthamine; is that
3 correct?
4 A. That is correct.
5 Q. And neither you nor Dr. Gershon, in deciding what
6 to try with your patients, decided to try cholinesterase
7 inhibitor at this time; is that correct?
8 A. Well, let me explain that further, if I can, and
9 that is that I did actually a study at the University of
10 Michigan, as I said earlier, with Lecithin alone in
11 normal people that were senile that didn't work. Dr.
12 Gershon knew of that and he thought that we should proceed
13 further. I agreed with the fact that he thought it might
14 be an interesting idea to do combination therapy and
15 that's what we actually did.
16 Q. It was an interesting idea, but you were treating
17 patients. You were interested in helping patients; is that
18 correct?
19 A. Of course. That's why we did the study.
20 Q. Let me --
21 A. Which was a research award funded by the State of
22 Michigan to do this.
23 Q. Let me show you another piece of work.
24 MR. SIPES: Approach the witness, your Honor?
25 THE COURT: Yes, you may.

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1 like effects as well as for a variety of central nervous
2 system disorders.
3 A. That is correct.
4 Q. You described the primary uses of galanthamine at
5 that time as being for myasthenia gravis and as an
6 antagonist of curare?
7 A. That is correct.
8 Q. Now, if you will turn to the conclusions -- I'm
9 sorry, to your review of the pharmacokinetics... This
10 is on Page 300 and 301.
11 A. I have it.
12 Q. Now, I think you testified that on the basis of
13 your review, you had come up with a serum half-life of
14 about four hours; is that correct? This morning, did
15 you suggest about a four-hour duration?
16 A. You're confusing human versus rat information. I
17 don't know what you are referring to.
18 Q. You do describe in your pharmacokinetic section
19 some work by Westra that showed an elimination half-
20 life of 264 minutes; is that correct?
21 A. That's correct. You divide by 60. That's 4.4
22 hours. That's from my head.
23 Q. Right. But that four-hour estimation, that comes
24 by work from Westra?
25 A. Correct.

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1 Q. Westra was published in 1986, after Dr. Davis had
2 applied for a patent; correct?
3 A. That is correct.
4 Q. But even on the basis of that additional information,
5 and we'll need the next page, the last paragraph before
6 summary. Even with that Westra work, you state,
7 Especially clear, however, from their pharmacokinetic
8 analysis is the fact that galanthamine is not a very
9 long-acting compound; correct?
10 A. That's correct. Still is true today.
11 Q. And the Westra work that you are citing is work in
12 humans; is that correct?
13 A. Correct.
14 Q. Now let's look at the summary.
15 Your summary is, although less potent than
16 physostigmine and with a similar duration of action, it
17 is claimed to be less toxic. Galanthamine deserves
18 further study as a possible indirect cholinergic agonist
19 treatment of the cognitive deficits in Alzheimer's
20 disease.
21 A. Correct.
22 Q. You viewed it as it has potential drawbacks?
23 A. I pointed out it's not long-acting.
24 Q. You pointed out although it has those drawbacks,
25 it's claimed to be less toxic?

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1 This was a brief study, so I don't know --
2 Q. But the 1971 Cozanitis article that I discussed
3 with Dr. Levy yesterday, that one you did put in your
4 report?
5 A. That's an important article comparing the two in
6 humans.
7 Q. And if you will turn to the next page, the Stojanov
8 (phonetic) article on the use of galanthamine as an
9 antidote for curare symptoms, that you also cited, is that
10 correct?
11 A. Yes.
12 Q. You cited with I guess the Russian spelling with
13 the Y rather than the J?
14 A. Yes.
15 Q. Let me ask you to look at the Bhasker article, which
16 is -- I'm not sure which one. It's DX-483.
17 You testified at deposition, did you not, that
18 in order to connect galanthamine to Alzheimer's disease
19 with regard to Bhasker, you're going to have to know the
20 whole cholinergic story as it relates to senile dementia
21 of the Alzheimer's type, correct?
22 A. Yes.
23 Q. And Bhasker himself never discusses Alzheimer's
24 disease by name, is that correct?
25 A. I remember the year. '74. What's going on? Put

EXHIBIT 3

1 A. Oh, I mean, it was a death sentence. I mean,
2 without even anything we could do to help her to make it
3 any easier.
4 Q. All right. What did you do after you finished your
5 residency?
6 A. I did a fellowship in endocrinology and metabolism
7 at Stanford.
8 Q. And during what period of time did you do your
9 fellowship at Stanford?
10 A. July of '75 to June of '77.
11 Q. Now, you used the words endocrinology and
12 metabolism. Let's just focus on endocrinology. What is
13 that?
14 A. Endocrinology is the study of hormones and glands.
15 Q. And what is neuroendocrinology?
16 A. Neuroendocrinology is the relationship of the brain
17 to the pituitary gland, the master gland, which is right
18 behind your nose, between your eyes, and then the
19 pituitary glands control over the other glands farther
20 down in your body.
21 Q. Now, had your interest in the connection between
22 the brain and hormones and glands in the body existed
23 prior to your fellowship?
24 A. It existed since I was a child.
25 Q. And can you date your first experience when you

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1 became interested in what you subsequently learned was
2 endocrinology, that connection between the brain and the
3 hormones?
4 A. Well, either I first learned it in school or I used
5 to take the train by myself into the city and go to the
6 museum of natural history. Maybe 11, 12 years old, I'm
7 not sure. And they had an exhibit there on the pituitary
8 gland and hormone diseases and they said the pituitary
9 gland never secreted more than a teaspoon of anything in
10 its whole life but it had extraordinary effects on
11 people. With too much growth hormone, people could be
12 a giant or they could be a midget if they didn't have
13 the growth hormone.
14 If the pituitary gland controlled the system
15 and made so much cortisol, they could be curbinol,
16 which meant they had a big round middle and skinny arms
17 and legs. There was picture of a woman who became
18 hypothyroid with her eyes bugging out.
19 I also used to go when I was there to an
20 exhibit that I think showed evolution from apes until
21 man and there was a series of brains along one wall in a
22 case and I was fascinated to look at the brains because
23 I understood by this point that my brain was made up of
24 nothing but brains, I mean nothing but atoms. And that
25 I appreciated that what the thing I was looking at was

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1 something I still don't even quite appreciate. You know,
2 understand.
3 Q. Now, coming forward in time, did you have an
4 opportunity during your fellowship to be involved in a
5 study that was neuroendocrine?
6 A. Yes, I did a study with the Chairman of the
7 Department of medicine.
8 Q. Can you describe that, please?
9 A. He was convinced that there could be men who would
10 have a low testosterone for a reason that had to do with
11 something in their brain, some sort of defeat or
12 depression or something. I think that stemmed from,
13 among other things, a study in military recruits years
14 earlier that showed that their testosterone went down
15 during basic training or the testosterone would go down
16 if they lost a fight relative to another animal.
17 Q. And did that -- were you able to conclude that
18 study during your fellowship or did you leave your
19 fellowship before it was done?
20 A. Well, we didn't conclude it, but what we did do was
21 we obtained a hormone from -- we obtained from a drug
22 company a hormone that came from the lower part of the
23 brain, the hypothalamus, that then stimulated the
24 pituitary gland to make luteinizing hormone
25 which goes to the testes and makes testosterone. We

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1 administered that hormone as a trial to a series of men
2 to see how well their pituitary glands were working and
3 how well their testes were working.
4 So if those things were working right, we
5 could conclude the problem was in the brain somewhere
6 north of the pituitary and, no, we didn't actually get
7 enough subjects to finish the study.
8 Q. All right. Now, as we begin to get to your patent
9 and your invention, though, can you tell us what is that
10 process in effect you have just described by which a
11 physician attempts to determine from hormone output in
12 the blood what's going on in the brain?
13 A. Well, the process was partially used in the study
14 that was done at Stanford, but it had been much more
15 used in a study of schizophrenia hormones to try and
16 understand what the chemical was that they changed in
17 the brain and that was called the neuroendocrine window.
18 Q. And why, I know it's breaking it down a little
19 bit into each of three parts. But why does -- did
20 science come to name that process the neuroendocrine
21 window?
22 A. Okay. Neuro is neurons. That's the brain.
23 Endocrine is the hormone system. And what we were doing
24 was using the hormones, the hormone system, to try and
25 get a picture into the brain, to see what was happening

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1 to brain chemicals which might be controlling the hormones
2 we could measure.
3 Q. All right. Now, did there come a time after,
4 either during or after your fellowship in the late 1970s,
5 when you received a request from your husband, let's take
6 it a step at a time, to help with the neuroendocrine window?
7 A. Yes. Because he was a psychiatrist, he knew about
8 the neuroendocrine window that related schizophrenia
9 drugs to dopamine, the brain chemical of most interest
10 in schizophrenia. He was now studying a new brain
11 chemical, acetylcholine, one that had not been that
12 much studied.
13
14 Q. So we can be clear now, your husband's name?
15 A. Kenneth Davis.
16 Q. That's Kenneth Davis that you're married to now?
17 A. Yes.
18 Q. He was your husband in the later 1970s; correct?
19 A. Correct.
20 Q. What work was your husband doing? And as part of
21 that work as you understood it, did he ask you for help
22 in dealing with your knowledge of the neuroendocrine
23 window?
24
25

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1
2 A. He wanted to manipulate acetylcholine levels in the
3 brain, but he wasn't sure that the drugs he had to try
4 and do that would really try choline acetyl levels. He
5 said to me if I make acetylcholine go up, can you tell
6 me a way I will know of that without being able to
7 measure acetylcholine in the brain, which couldn't be
8 done. Can you tell me how hormones will change if I
9 really can increase acetylcholine in the brain.
10 Q. All right. So he was trying to determine what was
11 going on in the cholinergic brain and asked you if you
12 could help him with some tool that would be able to tell
13 if there was activity based on what was going on in
14 hormones that could be measured in blood. Fair enough?
15 A. He wanted a parallel readout.
16 Q. All right. Now, before we get to the neuroendocrine
17 window tool that you designed -- oh, by the way, you are
18 not claiming to have invented the neuroendocrine window,
19 are you?
20 A. No.
21 Q. But is the neuroendocrine window a tool you used
22 ultimately to make your invention and learn and conceive
23 of the fact that galanthamine could be used to treat
24 Alzheimer's disease?
25 A. Yes.

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1 So from my point of view, I mean, I thought
2 people were just ignoring an important part of the
3 cholinergic system and a part that, in my experience,
4 probably played an important role in restoring
5 Alzheimer's patients' functions, because I used to smoke.
6 Q. All right. Why don't I have you resume the stand,
7 then. We're getting a little ahead of ourselves and I
8 will back up now to the tool that you helped you develop
9 for your husband.

10 (At this point the witness then resumed the
11 witness stand.)

12 BY MR. PAPPAS:

13 Q. Now, did you also develop a diagram that would
14 assist us in understanding the neuroendocrine window
15 approach that you used?

16 A. I did, but can I make one more comment about that?

17 Q. Absolutely.

18 A. Alzheimer's isn't a disease of memory. It's a
19 disease of learning.

20 Q. Okay. Let's stop right there. That's an important
21 concept.

22 Will you explain to us and to the Court, what
23 do you mean when you say Alzheimer's is not a disease of
24 memory, it's a disease of learning? What does that mean?

25 A. When -- well, I will tell you about a specific

1 pay attention, I couldn't get the material, right?

2 A. Right.

3 Q. So you're telling us in Alzheimer's, it's the
4 inability to have attention and cognitively learn the
5 information that then prevents you from ever having,
6 being unable to have a memory of something; isn't that
7 true?

8 A. Well, yes, I think attention is an important part
9 of learning.

10 Q. All right. Are we ready to move to the
11 neuroendocrine window now?

12 A. All right.

13 Q. Okay.

14 MR. PAPPAS: Can we put that up, please?

15 BY MR. PAPPAS:

16 Q. Now let's back up to the tool that you developed
17 at the request of your husband that you then used later
18 to make your invention.

19 What is disclosed here in terms that will
20 help us understand the basic fundamental principles of
21 the neuroendocrine window?

22 A. Okay. The purpose of the neuroendocrine window
23 was to be able to draw blood and infer and measure a
24 hormone and infer what had been going on with brain
25 chemicals.

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1 study. I mean, Alzheimer's patients can't learn new
2 information, but once you get them to learn it, they
3 remember it as well as normal and that's why an
4 Alzheimer's patient can tell you what happened after
5 World War II but can't tell you what they had for
6 breakfast. They didn't have Alzheimer's at the end of
7 World War II. They had plenty of acetylcholine. They
8 could lay down learning and now, even though they don't
9 have acetylcholine, they can remember it. They can
10 access that memory.

11 That's not true of breakfast because what
12 they had for breakfast, they had no acetylcholine. They
13 didn't lay down the learning. And they can no longer,
14 and so they can't access it. You actually don't need
15 acetylcholine to recall.

16 Q. So --

17 A. But memory is a good enough word for that.

18 Q. That's fine. Memory is the ability to recall
19 something you've learned. Fair enough?

20 A. Yes.

21 Q. But is what you are telling us, though, is that
22 attention, which is associated with the nicotinic
23 receptor, is very important to learning?

24 A. You can't learn if you're not attending.

25 Q. Or as they used to tell me in class, if I didn't

1 Now, let me see. Okay.

2 Over here we show blood being drawn, but go
3 back a little ways. We get to the adrenal gland-- The
4 adrenal cortex, the outside part of the adrenal gland
5 on top of the kidney makes cortisol. If we find cortisol
6 in the blood, we know it has come from the adrenal cortex.

7 If the adrenal cortex secretes cortisol, we
8 know it has been stimulated by the pituitary gland,
9 because the pituitary gland makes adrenocorticotrophic
10 hormone which then causes cortisol secretion. If the
11 pituitary gland makes ACTH, we know it has been
12 stimulated by the hypothalamus, groups of cells at the
13 base of the brain which made CRF, corticotropin
14 releasing factor. Corticotropin releasing factor has to
15 be stimulated to make ACTH.

16 We know that a stimulus for CRF secretion
17 is acetylcholine operating via a nicotinic receptor.

18 So we know that if you give some kind of
19 cholinergic drug and you get cortisol in one arm and
20 you get cortisol in the other arm, it has followed this
21 pathway. That acetylcholine nicotinic pathways have
22 been stimulated.

23 Q. All right.

24 A. That's only true for one aspect of cortisol
25 secretion. That's true for basal.

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1 Q. What you ultimately determined on the way to making
2 your invention is that cortisol would be a good marker
3 for whether or not more acetylcholine was active in the
4 brain; right?

5 A. That's right.

6 Q. All right.

7 Q. Now, let's slow down just one second.

8 Are there different -- I may get the
9 terminology wrong, but are there different types of
10 cortisol in our body?

11 A. There are different situations under which cortisol
12 is secreted.

13 Q. Okay. Let's discuss, I think, three of them. All
14 right?

15 A. Okay.

16 Q. Okay. What are the three levels of cortisol? And
17 tell us what the significance is of each of those three
18 levels, those three levels of cortisol as a marker for
19 particular activity. Okay?

20 A. Yes. We always have a low level of cortisol.
21 That's called basal cortisol levels.

22 If you -- that's under the control of the
23 nicotinic synapse in the brain. If basal cortisol is
24 raised by a drug you give, that has happened based on
25 the nicotinic cholinergic pathways.

1 A. So since we know that muscarinic blockade wipes
2 it out, we know it's mediated through the muscarinic
3 cholinergic system.

4 Q. What's the third aspect of cortisol that became
5 important to you ultimately making your conception?

6 A. It's a complicating factor. It's that nonspecific
7 stress can cause cortisol release as -- along with the
8 release of other hormones.

9 Q. When you say nonspecific, are you saying that is
10 not necessarily associated with activity in the brain?

11 A. Yes, probably a big operation could do it.

12 Q. All right. So it could be from stress anywhere in
13 the body? Correct?

14 A. I would think so.

15 Q. What about stress caused by a trial? What might be
16 happening to my cortisol level? Is it stress level or
17 one of the other effects?

18 A. No. I think it's not that stressful for you.

19 Q. I guess we'll see.

20 All right. Moving along here, ultimately,
21 let's go back to the neuroendocrine window.

22 Ultimately, were you able to give your
23 husband the tool, the help that Ken Davis asked for to
24 do his physostigmine experiments, applying the
25 neuroendocrine window, so he could make measurements?

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1 Q. This is something you came to learn; is that
2 correct?

3 A. Right.

4 Q. All right. So let's back up a slide.

5 The basal cortisol nicotinic receptor; right?

6 A. That's right.

7 Q. All right.

8 A. It cannot be made to happen with a muscarinic
9 stimulus.

10 Q. All right. What other level of cortisol?

11 A. Okay. Another aspect of cortisol secretion is that
12 sometime in the middle of the night, you begin to secrete
13 a little bit of cortisol, which then goes up very high to
14 the time you wake up and remains high for a bit of the
15 morning and then comes down. That is called the diurnal
16 rise of cortisol or the Circadian rise of cortisol.

17 Q. Do we all have that?

18 A. We all have that.

19 Q. All right. And which receptor system is diurnal
20 cortisol associated with?

21 A. That's due to acetylcholine operating on a
22 muscarinic receptor and it's not an on-line event.
23 Muscarinic blockade six hours before the expected
24 diurnal rise in cortisol wipes it out.

25 Q. All right.

1 Were you able to do that?

2 A. Yes.

3 Q. Okay. How was he able to use your formulation of
4 the neuroendocrine window to assist him in his research?
5 And then we'll get to your invention.

6 A. He gave physostigmine infusions to young Stanford
7 students to see if he could make them smarter and I told
8 him what to measure in the bloods, what hormones to
9 measure, and we got results that enabled us to assess
10 how much nicotinic cholinergic stimulation physostigmine
11 had produced in those patients, in those students in the
12 brain.

13 Q. All right. Now, for your research, in connection
14 with your research, in making your invention, what were
15 you able to conclude about what was going on in the
16 brain if cortisol went up?

17 A. If you simply gave an infusion of a drug and
18 cortisol went up, you had to have completed that whole
19 pathway that you see there. It's the yellow line,
20 starting in one arm where you give the drug. It would
21 have successfully increased acetylcholine in the brain,
22 gone through the nicotinic receptor, ultimately
23 resulted in cortisol you could measure in the other arm.
24 So if we got cortisol out of this arm, we knew we had
25 activity here, acetylcholine and nicotinic receptor in

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1 the brain.
2 Q. Are you saying I, Bonnie Davis, came to that
3 conclusion myself?
4 A. I, Bonnie Davis, came to that conclusion myself
5 and then told --
6 Q. All right.
7 A. -- other people.
8 Q. Now, when did it first occur to you that
9 galanthamine would work as a treatment for Alzheimer's
10 disease?
11 A. In Hawaii, on the morning I was presenting the
12 hormone results from the physostigmine study in Stanford
13 students.
14 Q. And do you remember a particular event that caused
15 you to begin to, quite frankly, piece together your
16 conception that galanthamine might work for Alzheimer's
17 drugs, for Alzheimer's disease?
18 A. I read the Cozanitis '74 article on that morning.
19 Q. All right. Let me ask you to take a look at it.
20 It's Plaintiffs' Exhibit 829.
21 Do you have it there in your binder or your
22 red well? It will be behind a tab, Dr. Davis, that
23 says 829.
24 A. Okay.
25 Q. Do you have it?

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1 A. Yes.
2 MR. LOMBARDI: What number?
3 MR. PAPPAS: Plaintiffs' 829.
4 MR. LOMBARDI: Thank you.
5 BY MR. PAPPAS:
6 Q. Do you have it there?
7 A. Yes.
8 Q. Take your time.
9 A. Okay.
10 Q. All right?
11 A. Yes.
12 Q. Is that the Cozanitis paper, Plaintiffs' Exhibit
13 829?
14 A. Yes.
15 Q. All right.
16 MR. PAPPAS: I don't believe that has been
17 moved into evidence, your Honor, but I would move it in.
18 MR. LOMBARDI: No objection.
19 THE COURT: Thank you.
20 DEPUTY CLERK: So marked.
21 *** (Plaintiffs' Exhibit No. 829 was received into
22 evidence.)
23 BY MR. PAPPAS:
24 Q. Doctor, I want to take this one step at a time.
25 Tell us from your review of the Cozanitis

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1 paper, what did Dr. Cozanitis do? Let's just take it
2 one step at a time.
3 What did he do as reported in this article?
4 A. He gave galanthamine for its usual use of being
5 given after surgery, to reverse curare. He measured
6 cortisol before he gave galanthamine and then for a period
7 of time afterwards.
8 Now, half the patients in the study got
9 galanthamine and the other piece got neostigmine, a
10 cholinesterase inhibitor, which does not get into the
11 brain.
12 Q. All right.
13 A. Principally doesn't.
14 Q. And the patients, some of which he gave galanthamine,
15 some of whom he gave neostigmine, were they otherwise
16 normal or were they patients suffering from Alzheimer's
17 disease?
18 A. They were normal women.
19 Q. Normal women. Okay.
20 And what results did he report on giving
21 galanthamine to some normal women and neostigmine to
22 other normal women?
23 -- --
24 A. Galanthamine caused a sustained rising in cortisol
25 which went on for at least six hours. But there was no

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1 rise in cortisol in the women given the neostigmine
2 Q. What conclusion did Dr. Cozanitis reach, if any,
3 about why some women had their cortisol levels go up?
4 -- --
5 A. He thought it was a stress response.
6 Q. Now, did he cite in his article to the findings of
7 any other person who had done work prior to him with
8 galanthamine?
9 A. Yes. He cited Naumenko.
10 MR. PAPPAS: Can we have up Page 167, Matt?
11 I'm sorry. Page 167. Cozanitis. And can you highlight
12 the portion around Naumenko, Matt. Right here
13 (indicating).
14 BY MR. PAPPAS:
15 Q. Now, who is the person who also did some work with
16 galanthamine that's referred to by Dr. Cozanitis?
17 Highlight it beginning with the word this,
18 please.
19 Who was that, Dr. Davis?
20 A. Who was he?
21 Q. No. Who is the man?
22 A. Naumenko.
23 Q. And what had Naumenko done as reported by Dr.
24 Cozanitis?
25 A. Naumenko thought that the reason cortisol went up

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1 when he gave galanthamine was that galanthamine was
2 stressful to the body.
3 Q. And --
4 A. And it was the stress in the body that caused
5 cortisol to go up.
6 Q. And what study had Naumenko done?
7 A. Naumenko gave galanthamine and cortisol went up,
8 but he said that's a stress response. So he decided to
9 cut off the body from the brain. He made a cut right
10 through the mid-brain, so that messages from the body
11 could no longer go up to the brain.
12 Q. So this isn't too gruesome now, Naumenko is doing
13 this to guinea pigs. That's bad enough, but he was
14 working with guinea pigs.
15 A. Still gruesome.
16 Q. I agree.
17 In any event, what did he find?
18 A. He found that once the mid-brain transection had
19 been done, galanthamine didn't produce much of a further
20 rise in cortisol.
21 Q. Okay. And so what conclusion did Naumenko draw
22 about why the galanthamine caused arise in cortisol in
23 guinea pigs?
24 A. He thought it was a nonspecific stress based on
25 stimulation of nerves in the periphery, below the neck.

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1 Q. And what conclusion did Dr. Cozantis draw about
2 why the cortisol went up in normal women after having
3 been administered galanthamine?
4 A. He ascribed it to the analeptic or sort of exciting
5 action of galanthamine producing some stress and
6 excitement and so he thought, okay. It's a stress
7 response.
8 Q. All right.
9 A. Nonspecific.
10 Q. All right. Now, so Cozantis says galanthamine
11 causes cortisol to go up due to stress, in women.
12 Naumenko says its guinea pigs, goes up due to stress.
13 Did you agree with those conclusions?
14 A. No.
15 Q. What conclusion did you reach?
16 A. I knew it was a specific central stimulation of the
17 nicotinic pathway.
18 Q. Now, how did you know as part of your making your
19 invention that although these men were reporting that
20 galanthamine caused an increase in cortisol due to
21 nonspecific stress, how did you know that it was not
22 that, but that it was actually action through the
23 nicotinic pathway of the brain?
24 A. Well, I knew that if you took the hypothalamus out
25 of a series of rats and you added acetylcholine to the

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1 little Petri dish in which they were, that that would
2 cause the secretion of CRF, corticotropin releasing factor,
3 which is at the top of the neuroendocrine pathway there.
4 I knew that you could block the effect of acetylcholine
5 with various compounds that blocked specifically
6 nicotinic receptors and I knew that when you tried to
7 get CRF out of those hypothalami in the Petri dish with
8 bethanicol, which is a specific stimulator of muscarinic
9 receptors, it didn't work.
10 There was also work done in rats in a
11 non-stressed state in which physostigmine was able to
12 raise cortisol and that could be blocked by the same
13 compounds which block only nicotinic receptors, classic
14 nicotinic receptor blockers. They're not all
15 anti-cholinergic. The name seems to be different.
16 Q. All right. And we have covered already the
17 importance of the nicotinic system to attention; is that
18 correct?
19 A. Yes.
20 Q. All right. Now, what was it, then, that caused you
21 ultimately to conclude that galanthamine would be
22 effective in treating Alzheimer's disease?
23 A. Well, to start with, I was never comfortable with
24 the fact that the field was predominantly muscarinic.
25 Acetylcholine had, to my knowledge, two functions, and

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1 they were both important in cognition, and if a person
2 got Alzheimer's disease and had no acetylcholine, I
3 didn't think it would be enough to simply replace the
4 nicotinic, the muscarinic component. I thought it was
5 very important to make sure that you replaced what was
6 missing, which was both nicotinic and muscarinic aspects
7 of acetylcholine.
8 And then I saw this drug, therefore, it was
9 a cholinesterase inhibitor, and so it was important to
10 me to use a drug like that.
11 But this drug worked. I wasn't testing the
12 memory system in brain. I was testing the neuroendocrine
13 system, but this drug got into the brain. It acted on a
14 brain system controlled by acetylcholine. It produced a
15 clear output in a majority of patients. It lasted for
16 an amount of time that would make sense for something
17 that could be a drug, could be a medication. And there
18 was no special comment about using it.
19 They used this all the time and I thought
20 this this is -- this is the way we need to treat
21 Alzheimer's.
22 Q. All right. Let's go back to the first drawing. I
23 want to point something out.
24 I want to follow up on one of your -- parts
25 of your testimony.

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1 You've been here for quite a bit of the --
 2 you've been here since the opening of trial; correct?
 3 A. Yes.
 4 Q. And you heard Dr. Levy testify; correct?
 5 A. Yes.
 6 Q. And you heard him talk about how he has been totally
 7 focused on the muscarinic system, muscarinic agonist;
 8 right?
 9 A. Yes.
 10 Q. And as of 1986, when you conceived of your invention,
 11 where was everybody looking?
 12 A. The field was really focused on the muscarinic
 13 system. They had a muscarinic model.
 14 When -- I mean, when I submitted this patent,
 15 I certainly wasn't sure, and a lot of other people
 16 weren't sure that cholinesterase inhibitors would ever
 17 work. They would speculate we may have to go right to
 18 agonists if the muscarinic receptor, tests that were
 19 developed left out attention.
 20 There was a real predominance of focus on the
 21 muscarinic --
 22 Q. It's the analysis you've just given us in your two
 23 prior answers, is that what led you to conclude that
 24 nicotinic was the way to go?
 25 A. I thought it was very important and we had to cover

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1 it.
 2 Q. Now, can you turn your attention to your patent,
 3 Dr. Davis, and specifically there's a description of a
 4 scopolamine model in your patent.
 5 Do you see that on Column 1, Lines 29 through
 6 34?
 7 A. Yes.
 8 Q. All right. Now, there has been some testimony in
 9 this court about scopolamine induced amnesia model.
 10 Did you believe when you were doing your work
 11 that the scopolamine model would help at all in solving
 12 Alzheimer's? Was it a good model for Alzheimer's
 13 disease?
 14 A. To me, it was missing half the story.
 15 Q. What do you mean, it was missing half the story?
 16 A. Well, it was missing the nicotinic and scopolamine
 17 has effects in blocking the muscarinic that you don't
 18 see in Alzheimer's patients. Scopolamine causes
 19 dilatation of pupils. Alzheimer's patients don't have
 20 dilated pupils. It causes sedation. Alzheimer's
 21 patients don't have a disturbance of consciousness.
 22 People would give scopolamine for a short period of time
 23 and see what could reverse it. Blocking a receptor for
 24 a few hours is not the same as having a system which is
 25 chronically under stimulated.

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1 Q. Did galanthamine have muscarinic effects?
 2 A. Some. Not -- some.
 3 Q. But how would you compare the side effects of
 4 galanthamine, if any, with the side effects that were
 5 traditionally associated with muscarinic agents? Such
 6 as physostigmine?
 7 A. Different. Different side effects.
 8 Q. Describe the side effects on drugs that were
 9 primarily muscarinic.
 10 A. Muscarinic drugs make people sweat, have abdominal
 11 cramps, have diarrhea, have nausea and I think Dr.
 12 Domino told us also urination, defecation, salivation.
 13 Q. And are those side effects typically associated
 14 with nicotinic?
 15 A. Those are mostly muscarinic.
 16 Q. All right. And I take it those are side effects
 17 you want to avoid if you want to give a drug for
 18 Alzheimer's; is that right?
 19 A. Yes.
 20 Q. All right. Now, in 1986, when you made your --
 21 filed for your patent, how did galanthamine compare to
 22 other cholinesterase inhibitors in terms of its
 23 strength? Weak, strong, neutral? How was it?
 24 A. Galanthamine was in one study that I'm aware of a
 25 hundred times weaker than physostigmine in muscle and

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1 about 30 times weaker in brain.
 2 Q. Now, were you concerned that galanthamine was a
 3 weak cholinesterase inhibitor, as much as a hundred
 4 times less potent than physostigmine?
 5 A. No.
 6 Q. Why not?
 7 A. Because it produced a cholinergic output from brain,
 8 because it raised cortisol. And I knew the pathway and
 9 so it was -- it could be made to increase cholinergic
 10 transmission in brain. I mean, physostigmine didn't do
 11 that in the Stanford study. There was no elevation of
 12 basal cortisol unless people got sick.
 13 Q. All right. Now, prior to filing for your patent
 14 application, had you attempted to get galanthamine, the
 15 drug?
 16 A. I had.
 17 Q. All right. Let me ask you to look at Plaintiffs'
 18 Exhibit 121.
 19 And while you're at it, Dr. Davis, it might
 20 be helpful to take out Plaintiffs' Exhibit 122 and 123,
 21 because I'm going to go through them together because
 22 they really all are about your efforts.
 23 A. Okay.
 24 Q. Let me know when you have 121.
 25 A. Got it.

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1 Q. Can you identify this document?
2 A. Yes. It's a letter I wrote to Dr. Cozanitis.
3 Q. All right. And let me ask you to direct your
4 attention to what I have had marked for identification
5 as Plaintiffs' Exhibit 122. Can you identify that
6 letter?
7 A. Yes.
8 Q. And what is that?
9 A. It's a response from Dr. Cozanitis.
10 Q. Okay. And what is the date of the response from
11 Dr. Cozanitis to you in Plaintiffs' Exhibit 122?
12 A. October 8th, 1980.
13 Q. Okay. I know that Plaintiffs' Exhibit 121 is
14 undated, but does the response from Dr. Cozanitis help
15 you approximate for us the time period of your letter
16 to him asking for galanthamine?
17 A. Yes. It must have been prior to that.
18 Q. All right.
19 MR. PAPPAS: Your Honor, I would move 121 and
20 122 in.
21 MR. LOMBARDI: No objection.
22 THE COURT: Thank you.
23 DEPUTY CLERK: So marked.
24 *** (Plaintiffs' Exhibits No. 121 and 122 were
25 received into evidence.)

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1 Q. And did you ever get a response from Dr. Jordanov?
2 A. No, I didn't.
3 Q. Did you make further attempts to get galanthamine?
4 A. Yes.
5 Q. And what was your next attempt to get galanthamine?
6 A. I put \$50 in an envelope and sent it to Pharmacia
7 and asked them to send me however much that would buy.
8 Q. Did you get a response from them?
9 A. No.
10 Q. By the way, did you get your money back?
11 A. No.
12 Q. To your knowledge, was galanthamine available in
13 the United States at that time and specifically at that
14 time I'm talking about 1985, 1986?
15 A. To my knowledge, it wasn't.
16 Q. Did there come a time after your patent application
17 was filed when you were successful in obtaining
18 galanthamine?
19 A. Yes.
20 Q. All right. And how did that come about?
21 A. Sasha Mathe, who was in our group,
22 obtained it from I think Professor Cartovich (phonetic)
23 in Russia.
24 Q. Is this in 1986 sometime?
25 A. Yes. Well, yeah. I think so. '86 or early '87.

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1 BY MR. PAPPAS:
2 Q. What are you asking Dr. Cozanitis in Plaintiffs'
3 Exhibit 121?
4 A. I'm asking him for information on how to get
5 galanthamine.
6 Q. And what does Dr. Cozanitis write back to you in
7 Plaintiffs' Exhibit 122?
8 A. He writes that I should contact Pharmacia in
9 Bulgaria.
10 Q. And did you do that?
11 A. I did.
12 Q. Let me direct your attention to what I've had
13 marked for identification as Plaintiffs' Exhibit 123.
14 Is that a letter from you to Dr. Jordanov
15 in Bulgaria, dated March 16, 1983?
16 A. Yes.
17 MR. PAPPAS: I move it.
18 MR. LOMBARDI: No objection.
19 THE COURT: Thank you.
20 *** (Plaintiffs' Exhibit No. 123 was received into
21 evidence.)
22 BY MR. PAPPAS:
23 Q. What do you ask him?
24 A. I ask him how to purchase galanthamine for use in
25 my research.

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1 Q. Certainly.

2 A. He validated his paradigm with scopolamine.

3 Q. And what's the significance of that?

4 A. It wasn't the scopolamine model. You had to show

5 that something worked in scopolamine dementia.

6 Q. And what did Dr. Coyle report in Plaintiffs'

7 Exhibit 117 in the abstract about the results of his

8 studies on mice? Is there a sentence there particularly

9 that sums it up?

10 A. The final sentence.

11 Q. I think that does it.

12 A. Galanthamine's ability to reverse cognitive deficits

13 induced by NBM lesions and its comparatively long half-

14 life suggests it may be effective in treating the central

15 cholinergic deficits in Alzheimer's disease patients.

16 Q. How would you characterize the results? Positive,

17 negative or inconclusive?

18 A. They were clearly positive.

19 Q. All right. So now that you have your '318 patent

20 that was issued by the Patent Office and the animal

21 results of testing from Dr. Coyle, what did you do next

22 in your attempt to develop galanthamine as a treatment

23 for Alzheimer's disease?

24 A. I sent out a series of letters to drug companies

25 to assess their interest in licensing.

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1 Q. Well, were you not able, with your husband, to

2 develop galanthamine on your own?

3 A. That's right. We were not able to develop

4 galanthamine on our own.

5 Q. Simply put, you didn't have the funds or the

6 wherewithal to spend the kind of money it will take

7 to develop this drug; is that correct?

8 A. That's correct.

9 Q. All right. So did you assist my colleagues and I

10 in putting up what we'll call round one of your attempts

11 to find someone who would agree to license the '318

12 patent from you and pursue the development of

13 galanthamine for the treatment of Alzheimer's disease?

14 A. I was thinking about something else.

15 Q. I'm sorry. And my question perhaps suffered as

16 they sometimes do from being long.

17 Let me try to be briefer.

18 Did you help me prepare a chart that shows

19 the -- in one form, summary form, all your efforts

20 between 1987 and 1990 to find someone, a pharmaceutical

21 company, that would license the patent?

22 A. Yes.

23 MR. PAPPAS: Can we have that chart, please?

24 BY MR. PAPPAS:

25 Q. Now, Dr. Davis, we note on the chart that the dates

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1 hypothalamus in a petri dish you could get ultimately
 2 corticotropin factors to come out.
 3
 4 A. (Continuing) If you gave cholinergic drugs to
 5 non-stressed animals, block the muscarinic, you could
 6 get cortisol under nicotinic conditions. You could
 7 increase cortisol with nicotine in humans. And the
 8 Cozantitis articles were really very good. They were
 9 specific.
 10 Q. All right.
 11 A. They were as good a data in humans as you could
 12 have gotten from an animal study and that does not
 13 usually happen.
 14 Q. All right. Now, let me move forward in time.
 15 You told us yesterday that you had your
 16 conception about use of galanthamine for Alzheimer's
 17 disease in Hawaii. Can you give us the date? I forgot
 18 to ask you the date yesterday.
 19 A. It was either the end of August, beginning of
 20 September 1977, three weeks before my son was born.
 21 Q. Very well.
 22 And how was it that you happened to have
 23 Cozantitis and other papers with you on that trip?
 24 A. Yes. Well, that was the problem, because this
 25 baby was coming, and so before we left for Hawaii, I put

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1 studies? Indeed, did you do some work as part of those
 2 studies?
 3 A. Which one? I mean, the ones that were done at
 4 Stanford, no. I just -- I just -- I just added my
 5 section for him.
 6 Q. All right. But thereafter, were you involved in
 7 any of the physio studies?
 8 A. Yeah. Then I was involved in a medical way.
 9 Q. All right. Now, we've heard from Barr that your
 10 husband was working with physostigmine and ultimately
 11 physostigmine studied in Alzheimer's patients; correct?
 12 A. Yes.
 13 Q. All right. Now, but you've testified that as of
 14 1977, you conceived that galanthamine should be used for
 15 Alzheimer's disease; correct?
 16 A. Instead of physostigmine.
 17 Q. All right. Right. Did you follow these physio
 18 studies in that period between 1978 and 1986?
 19 A. Yeah.
 20 Q. And --
 21 A. To some degree.
 22 Q. All right. And what, if anything, did they tell
 23 you about your invention vis-a-vis what your husband
 24 was trying with physostigmine?
 25 A. Oh, that he would have had a much easier time if

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1 the crib together and I washed all the baby clothes and
 2 I rinsed them an extra time and I put the papers in a
 3 suitcase because that could wait and, you know, who
 4 knew what would happen in the next few weeks.
 5 Q. Well, was the Cozantitis and all of those other
 6 papers part of a much larger group of research you had
 7 been doing prior to that time?
 8 A. Recently, but prior to that time.
 9 Q. All right.
 10 A. There were a lot of papers that were reviewed.
 11 Q. Now, let's move forward.
 12 After your conception in 1977 that galanthamine
 13 would work, I want to cover the time period between 1978
 14 and 1986, when you filed your patent application. All
 15 right? Are you with me in terms of time?
 16 A. Yes.
 17 Q. All right. Now, you have been here in court and
 18 heard a lot of testimony about physostigmine studies and
 19 papers that were published by your husband in which your
 20 name appears. Do you recall that?
 21 A. Yes.
 22 Q. Okay. Were physostigmine studies being done in
 23 the late seventies, early eighties, by your husband?
 24 A. Yes. That's when they started.
 25 Q. All right. And did you follow the results of those

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1 he had done it my way.
 2 Q. Well, did his way work?
 3 A. No.
 4 Q. Okay. What happened --
 5 A. After -- that way never worked.
 6 Q. I understand. But to get, quite frankly, a little
 7 scientific, what was it in all the discussion you've
 8 given us yesterday about muscarinic and nicotinic
 9 systems, what was it you found out in these physio
 10 studies that did not work?
 11 A. Well, we measured hormones in that first study in
 12 Stanford students. Physostigmine never raised cortisol
 13 unless the subjects were stressed, in which case -- and
 14 threw up, or at least got very nauseated, in which
 15 case it raised cortisol, growth hormone and prolactin.
 16 And remember prolactin was my checker. And if that went
 17 up, then you couldn't describe the rise in cortisol to a
 18 specific nicotinic mechanism.
 19 Q. All right.
 20 A. So physostigmine didn't work in the tool that I
 21 set up.
 22 The tool was to test does physostigmine
 23 increase cholinergic transmission in the brain and
 24 using my tool, the test showed, no, it didn't.
 25 Q. And so what lesson did you draw with respect to

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1 your invention from the fact that the physo studies
2 failed?
3 A. That physostigmine was not good at doing what was
4 needed to treat Alzheimer's.
5 Q. All right. Now, let's come forward, then, to 1987,
6 when you began to interest pharmaceutical companies in
7 developing -- before I go there. We covered the
8 scopolamine model yesterday. Do you recall that?
9 A. Yes.
10 Q. And you told the Judge why you didn't think the
11 scopolamine model was a good model for Alzheimer's. Do
12 you remember?
13 A. Yes.
14 Q. All right. Well, what conclusions did you draw
15 in terms of your invention prior to filing for the
16 patent in 1986 by the fact that the scopolamine model
17 did not prove to be a good model for Alzheimer's disease?
18 What conclusions did you draw about your invention?
19 A. Well, weren't those separate? I mean, the
20 scopolamine model wasn't a good model and, I mean --
21 Q. And why wasn't it a good model for Alzheimer's
22 disease?
23 A. Well, as we spoke about, it was purely nicotinic.
24 It was more nicotinic than Alzheimer's disease. I mean,
25 excuse me. I was purely muscarinic and the muscarinic

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1 Q. And did you sign the license on behalf of a company
2 you had then called Intelligen?
3 A. Yes.
4 Q. Was it also signed by Doug Watson on behalf of
5 Ciba-Geigy?
6 A. Yes.
7 Q. Is this the license agreement that you entered
8 into with Ciba-Geigy in 1990 for the development of
9 galanthamine as a treatment for Alzheimer's disease?
10 A. Yes, it is.
11 MR. PAPPAS: Your Honor, I would move
12 Plaintiffs' Exhibit 305 into evidence.
13 MR. LOMBARDI: No objection.
14 THE COURT: Thank you.
15 DEPUTY CLERK: So marked.
16 *** (Plaintiffs' Exhibit No. 305 was received into
17 evidence.)
18 BY MR. PAPPAS:
19 Q. Now, did Ciba do any work pursuant to the license
20 agreement?
21 A. Yes.
22 Q. Okay. And what work did they do?
23 A. They did animal toxicology, one and two year, and
24 they did a clinical study.
25 Q. All right. And what were the results of those

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1 studies?
2 A. The toxicology was good and the clinical study
3 indicated to them that the drug would have efficacy.
4 Q. And when you say the drug, we're referring to
5 galanthamine, is that correct?
6 A. Yes.
7 Q. And they were studying it for the use in Alzheimer's
8 disease, correct?
9 A. Yes.
10 Q. Now, did there come a time when the relationship
11 with Ciba-Geigy came to an end?
12 A. Yes.
13 Q. Let me ask you to take a look at what we previously
14 had marked as Plaintiffs' Exhibit 467.
15 Can you get it there in your accordion file
16 of exhibits?
17 A. I have it.
18 Q. Can you tell us, first, before we -- before
19 referring to any contents, the date of the letter, who it
20 is from and who it is addressed to?
21 A. The letter is dated November 10th, 1993. It's
22 from Douglas G. Watson of Ciba-Geigy, President,
23 Pharmaceuticals Division. And it's addressed to
24 Intelligen Corporation, which is me.
25 Q. All right. And I take it you received this letter;

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1 with either the efficacy or the safety of galanthamine.
2 This was a business decision reflecting limited
3 development resources. It was well understood that
4 galanthamine, according to the results of Protocol 01,
5 promises to be an efficacious and, in comparison to
6 other treatments, a safe drug.
7 Q. Thank you.
8 Dr. Davis, I recognize here in reviewing my
9 notes, I failed to ask you, with respect to Plaintiffs'
10 Exhibit 173, which was the Mylan letter of rejection,
11 the one we just covered, do you recall that?
12 A. Yes.
13 Q. To your knowledge, has Mylan, the same Mylan that's
14 a defendant in this case, ever developed a successful
15 treatment for Alzheimer's disease?
16 A. Not to my knowledge.
17 Q. All right. Now, Dr. Davis, in our timeline, we're
18 at what point in time now that Ciba-Geigy has told you
19 they are terminating the studies?
20 A. The end of 1993.
21 Q. All right. Now, what did you do?
22 A. I had to start all over again.
23 Q. And what do you mean when you say you had to start
24 all over again?
25 A. I had to look for someone to continue galanthamine's

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1 development.
2 Q. And did you do that?
3 A. I did.
4 Q. All right. Did you assist my colleagues and I
5 in preparing a similar chart that we've seen already as
6 Plaintiffs' Exhibit 1397 that would reflect your efforts
7 to market your invention and interest a pharmaceutical
8 company in developing galanthamine from 1993, when Ciba
9 terminated the license, up till the time you had the
10 license with Janssen?
11 A. I did.
12 Q. Okay.
13 MR. PAPPAS: Can we have on the screen, please,
14 Plaintiffs' Exhibit 1398?
15 MR. PAPPAS: Your Honor, I realize I had not
16 handed up to your Clerk a copy of Plaintiffs' Exhibit
17 1397. It wasn't in your folder yesterday (handing
18 document to the Court).
19 Thank you.
20 BY MR. PAPPAS:
21 Q. Now, let me ask you to take a look at what we've
22 had marked for identification at this time, Dr. Davis,
23 as Plaintiffs' Exhibit 1398.
24 I will ask, first of all, was this prepared
25 in the same manner as the prior chart in terms of

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1 Q. And, to your knowledge, did Marion Merrell Dow
2 develop a successful treatment for Alzheimer's disease?
3 A. No, not to my knowledge.
4 Q. All right. Now, can we have Plaintiffs' Exhibit
5 1398?
6 I take it from this chart here that we've
7 had admitted that in November 1995, you have an entry
8 here that says Janssen license.
9 What does that mean?
10 A. The patent was licensed to Janssen.
11 Q. All right. Now, Dr. Davis, let me ask you to take
12 a look at Plaintiffs' Exhibit 329 that was admitted
13 yesterday, but it's also in your folder, and let me know
14 when you have it.
15 A. I have.
16 Q. Can you take a look at it?
17 A. Okay.
18 Q. Do you recognize it?
19 A. Yes.
20 Q. Okay. Is this, it was admitted yesterday, but just
21 to move things along, is this the license between
22 Synaptech and Janssen for the development of galanthamine
23 for the use in Alzheimer's disease?
24 A. Yes.
25 Q. All right. Now, what work did Janssen do with

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1 respect to galanthamine after this license agreement was
2 signed with Synaptech?
3 A. I guess the largest amount of work was to pivotal
4 clinical studies.
5 Q. And do you know what the results of those were?
6 A. Yes. They were positive.
7 Q. And do you know whether Janssen was able to obtain
8 FDA approval ultimately for galanthamine as a treatment
9 for mild to moderate Alzheimer's disease?
10 A. Yes.
11 Q. Do you know when it was approved by the FDA?
12 A. February 28th, 2001.
13 Q. Now, since 2001, can you approximate for us the
14 amount of sales Razadyne has enjoyed in the United States
15 due to prescriptions written by physicians?
16 A. Yeah. Basing my estimate on what Dr. Boghigian
17 said yesterday about the mid-eight hundreds about a year
18 ago, it would be about a billion now.
19 Q. All right. In other words, you're bringing the
20 numbers forward from Mr. Boghigian's testimony because he
21 was back in '06; is that correct?
22 A. Yes.
23 Q. All right. Now, subsequent to the approval and
24 marketing of Razadyne as a treatment for galanthamine,
25 Dr. Davis, have you, over the course of the last two to

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1 MR. PAPPAS: Can you blow that up for me or
2 highlight it?
3 BY MR. PAPPAS:
4 Q. You are referring to the Cozanitis studies here in
5 Column 1 of the patent; is that correct?
6 A. Yes.
7 Q. 1974 and 1980; is that correct?
8 A. Right.
9 Q. Now, in the patent, it reads, These studies showed
10 an increase in both plasma cortisol and plasma ACTH when
11 galanthamine was administered to patients together with
12 atropine.
13 Now, what does that tell somebody of ordinary
14 skill in the art who works in this field if they read
15 that with respect to nicotinic or muscarinic? Is it
16 nicotinic or muscarinic?
17 MR. LOMBARDI: Excuse me. I think that that
18 was a request for an opinion on a level of ordinary
19 skill in the art and this witness was never designated
20 as an expert, so I would object.
21 MR. PAPPAS: Your Honor, Mr. Lombardi has
22 gone through the patent in cross-examination and asked
23 this witness whether or not nicotinic was disclosed and
24 she told him that while the word wasn't there, the
25 concept was disclosed. I think I am entitled to explore

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1 on redirect just where that disclosure is to one of
2 ordinary skill in the art in her patent.
3 THE COURT: Well, I think basically that you
4 can explore her understanding and perhaps you can
5 explore what her understanding of one of ordinary skill
6 in the art, but certainly I won't accept this as an
7 expert opinion on what one of ordinary skill in the art
8 would --
9 MR. PAPPAS: Very well, your Honor. I'm
10 just trying to cover what she believes that's a disclosure
11 of.
12 THE COURT: Well, you can certainly explore
13 that.
14 MR. PAPPAS: Certainly.
15 BY MR. PAPPAS:
16 Q. What are you disclosing there, Dr. Davis?
17 A. When you give a cholinesterase inhibitor
18 together with a muscarinic blocker, you have a nicotinic
19 effect.
20 Q. Is that something you learned in medical school?
21 A. Yes.
22 Q. Now, let me ask you to direct your attention to
23 Column 2. Specifically, Lines 45 through 56.
24 Do you see that?
25 A. Yes.

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1 Q. All right. And specifically, I want to draw your
2 attention to -- this is a description of the animal
3 model; is that correct?
4 A. That's right.
5 Q. All right. And you see the words that were written
6 there, quote, a selective lesion is placed in the
7 subcortical nucleus, parentheses, nucleus basalis of
8 Meynert, close parentheses, with a resultant cortical
9 cholinergic deficiency, similar in magnitude to that
10 seen in early to moderate stage Alzheimer's disease.
11 Have I read that correctly?
12 A. Yes.
13 Q. Now, what are you telling or disclosing there?
14 A. Well, Alzheimer's patients are missing
15 acetylcholine in the cerebral cortex and we could model
16 that by destroying a nucleus in the brain that made the
17 acetylcholine for that part of the cortex, for the
18 cortex, and it would be about the same diminution of
19 acetylcholine that one would get in early to moderate
20 Alzheimer's disease.
21 Q. All right. Now, we've heard earlier testimony
22 about the scopolamine model.
23 Is this different, the model that talks about
24 the nucleus basalis of Meynert?
25 A. Oh, it's much better.

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1 Q. Is it different?
2 A. Yes.
3 Q. So it's different and better?
4 A. Yes.
5 Q. All right. Why?
6 A. Because here you're taking away acetylcholine, so
7 you're taking away all the effects of acetylcholine,
8 muscarinic and nicotinic, and it also has a chronic
9 effect. It's down the way it is in Alzheimer's disease
10 for a long period of time. It's not a one-shot deal.
11 Q. All right. Now, let me ask you to direct your
12 attention to Plaintiffs' Exhibit 699.
13 Do you have that up there with you?
14 (Pause.)
15 MR. PAPPAS: Your Honor, I don't believe it's
16 in her binder, but this Plaintiffs' Exhibit 699 was
17 admitted into evidence yesterday.
18 May I approach the give the witness a copy?
19 THE COURT: Yes.
20 MR. PAPPAS: 699.
21 MR. LOMBARDI: Just hold it up. Thank you.
22 I got it.
23 (Mr. Pappas handed an exhibit to the witness.)
24 THE WITNESS: Thank you.
25

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EXHIBIT 4

1 Q. Have you ever treated Alzheimer's patients?
2 A. Well, I managed Alzheimer's patients prior to the
3 time I became the Director of the Division of Child
4 Psychiatry in '82. This was primarily during my
5 residency and during my time as a faculty member,
6 running a clinic at Hopkins. I say manage because back
7 then there were no treatments.
8 Q. Have you ever done any Alzheimer's research?
9 A. Yes. I started my research in Alzheimer's disease
10 in about late 1978, and that continued to be a major
11 interest in my laboratory, neurobiology of Alzheimer's
12 disease, well into the nineties.
13 Q. What was the nature of your research?
14 A. Well, one of my first research interests was in
15 the neurobiology of neurodegenerative disorders, and
16 we discovered a method in which we could selectively
17 kill neurons in the brain in a way that was like
18 neurodegenerative disorders in humans.
19 The first disorder we looked at was
20 Huntington's disease and then that was in '76, and then
21 the papers came out showing that there was these
22 reductions in the markers for cholinergic neurons in
23 the cortex of individuals who died with Alzheimer's
24 disease.
25 The source of that innervation, that is

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1 where the cell bodies of those neurons were located,
2 was unknown at the time, although there was some
3 suggestion it might be in the base of the brain, the
4 nucleus basalis. We made the selective lesion in the
5 nucleus basalis in rats and this selected in rats the
6 cholinergic deficits that were seen in the brains of
7 individuals with Alzheimer's disease. That is, this
8 caused these neurons to die.
9 We subsequently showed in collaboration with
10 David Olten (phonetic) at Hopkins that these animals
11 exhibited deficits in working memory, much like
12 individuals in the early stages of Alzheimer's disease.
13 This became a particularly attractive model
14 superseding the scopolamine model because, number one,
15 scopolamine only blocked muscarinic receptors.
16 Number two, it was -- it was a temporary
17 blockade whereas this model literally recreated the
18 degeneration, pre-synaptic cholinergic neurons, which
19 affected any of the receptors, cholinergic and nicotinic
20 receptors, that would respond to acetylcholine.
21 Q. Did you use this model to test drugs for Alzheimer's
22 disease?
23 A. We did, we did study with physostigmine --
24 physostigmine with David Olten and then I was contacted
25 by Bonnie Davis.

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1 A. Oh, the first published work came out in the
2 proceedings for the meeting of neuroscience in the fall
3 of 1987.

4 Q. Have you recently published work?

5 A. Well, I -- I published a -- a review back in, I
6 think, the year 2001, looking at the possibility that
7 galanthamine might have, of course, altering effects,
8 and I just completed a review that was accepted for
9 publication in the Journal of Alzheimer's Disease on
10 galanthamine as an allosteric modulator of nicotinic
11 receptors.

12 Q. If you could turn to Tab 1 in the materials in
13 front of you, it should be Plaintiffs' Exhibit 1366.

14 A. Yes.

15 Q. Do you recognize Plaintiffs' Exhibit 1366?

16 A. Yes. It's my curriculum vitae.

17 MR. SIPES: Your Honor I'd move Plaintiffs'
18 Exhibit 1366 into evidence.

19 MR. GRACEY: No objection.

20 THE COURT: Thank you.

21 *** (Plaintiffs' Exhibit No. 1366 was received into
22 evidence.)

23 BY MR. SIPES:

24 Q. Do you believe you could be helpful to this Court
25 in understanding the state of the art with your expertise

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1 with Don Price, who was the head of neuropathology at
 2 Hopkins.
 3 Q. When was it published?
 4 A. 1983.
 5 Q. And you're one of the authors?
 6 A. I was the senior author, yes.
 7 Q. Is it a peer-reviewed article?
 8 A. Yes. This is a peer-reviewed article.
 9 Q. Was it an influential article?
 10 A. Well, it has been cited over 2,500 times in
 11 scientific literature.
 12 Q. Was it influential before 1986?
 13 A. Yes.
 14 MR. SIPES: I will move Plaintiffs' Exhibit
 15 663 into evidence.
 16 MR. GRACEY: No objection.
 17 THE COURT: Thank you.
 18 DEPUTY CLERK: So marked.
 19 *** (Plaintiffs' Exhibit No. 663 was received into
 20 evidence.)
 21 BY MR. SIPES:
 22 Q. The title of the article is Alzheimer's Disease, A
 23 Disorder of Cortical Cholinergic Innervation.
 24 What did you mean by that?
 25 A. Well, this article summarizes the evidence that

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1 among the neuronal systems that degenerate in Alzheimer's
 2 disease, the cholinergic neurons appear to be especially
 3 vulnerable. And then it goes on to discuss the implications
 4 of this with regard to potential treatment.
 5 Q. The defendants actually have referred to lots of
 6 things called the -- the cholinergic deficit hypothesis
 7 of Alzheimer's disease.
 8 A. Right.
 9 Q. How does your article from Science relate to the
 10 cholinergic deficit hypothesis?
 11 A. Well, I think it tries to take a balanced and
 12 tempered approach. It -- it points out the evidence that
 13 there is both cholinergic neurodegeneration and hypo
 14 function, particularly in the cortical limbic regions
 15 of the brain in Alzheimer's disease and degeneration of
 16 these basal for brain cholinergic neurons, but it also
 17 summarizes the rather, let's say, unsatisfying results
 18 from attempts to enhance cholinergic neurotransmission
 19 in Alzheimer's disease.
 20 Q. And let me first turn your attention to the first
 21 page, Plaintiffs' Exhibit 663, to the heading, Alzheimer's
 22 Disease.
 23 Do you see that?
 24 A. Yes.
 25 Q. And, first, the first sentence is a description of

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1 pre-senile dementia. I wonder if you could read that
 2 into the record?
 3 A. Sure. Pre-senile dementia of the Alzheimer's type
 4 is a rare disorder in which individuals, typically in
 5 their fifth decade, develop a progressive deterioration
 6 of cognitive functions clinically indistinguishable from
 7 senile dementia.
 8 Q. And this description of pre-senile dementia of the
 9 Alzheimer's type, is that an understanding of pre-senile
 10 dementia that a person of ordinary skill in 1986 would
 11 have had?
 12 A. Yes.
 13 Q. If we could scroll down a little bit, could you
 14 read the next sentence into the record?
 15 A. The demonstration that the pathological alterations
 16 in the brains of more than half of elderly demented
 17 individuals are similar to those found in the brains of
 18 patients suffering from the pre-senile form of
 19 Alzheimer's disease suggests that these are related
 20 disease processes.
 21 Q. Is this sentence referring to what we've in this
 22 courtroom come to refer to as senile dementia of the
 23 Alzheimer's type?
 24 A. That is right.
 25 Q. And are you describing senile dementia as a

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1 related disease process to pre-senile dementia?
 2 A. Yes.
 3 Q. Is that a view that a person of ordinary skill in
 4 the art would have had 1986?
 5 A. I believe that's the case.
 6 Q. Does the next sentence describe what the
 7 relationship is between those two diseases?
 8 A. Yes.
 9 Q. Could you explain what the next sentence is
 10 saying?
 11 A. It's basically saying that in both diseases, one
 12 sees these pathologic stigmata, that is the neuritic
 13 plaques and the neurofibrillary tangles.
 14 Q. Now, let me ask you to turn, if you would, to
 15 Page 1188 of the article.
 16 In the right-hand column, about -- it's the
 17 second full paragraph, there's a discussion of individuals
 18 with Downes Syndrome.
 19 Do you see that? The left-hand column. I
 20 apologize.
 21 A. Yes. It's halfway through the column, left-hand
 22 column.
 23 Q. That's correct.
 24 Could you read the first sentence into the
 25 record?

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1 A. Sure. Individuals with Downes Syndrome, Trisomy
2 21, often experience a progressive deterioration in
3 their limited cognitive abilities beginning at
4 approximately 30 to 35 years of age.
5 Q. And then the next sentence, if you would?
6 A. Brains of affected patients show neuropathological
7 changes virtually identical to those in AD, or Alzheimer's
8 disease.
9 Q. Well, what were you saying about individuals with
10 dementia and Downes Syndrome?
11 A. Well, this provides a very interesting genetic link
12 at that time. We were trying to figure out why neurons
13 die in -- what do the plaques entangles have to do in
14 Alzheimer's disease and it turns out that the gene that
15 encodes for the protein that ultimately creates the
16 amyloid and the plaques is located on chromosome 21.
17 And the problem with Downes Syndrome is they
18 have three copies of chromosome 21. And so they have an
19 extra copy of the gene that makes this protein that
20 ultimately is pathologically responsible for Alzheimer's
21 disease.
22 Just parenthetically, we're able to create
23 mice with the same problem and that helped us understand
24 the molecular mechanisms.
25 Q. Now, the dementia that individuals with Downes

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1 Syndrome get, is that a related dementia to Alzheimer's
2 disease?
3 A. Well, it's definitely related at a molecular level
4 and a pathologic level.
5 Q. So would a person of ordinary skill in the art in
6 1986 have viewed dementia in Downes Syndrome as a
7 dementia related to Alzheimer's disease?
8 A. I think those who are on the cutting edge.
9 Q. And were there any other dementias in 1986 that were
10 characterized by plaques and tangles?
11 A. No.
12 Q. Let me ask you, then, to turn back to the first
13 page, on the right-hand column, and in the right-hand
14 column you'll see there's a section, cholinergic neurons
15 and Alzheimer's disease.
16 Do you see that?
17 A. Yes.
18 Q. What are you describing in that section?
19 A. Well, I'm describing the evidence that implicates
20 hypo function of cholinergic neurons in the path of
21 physiology or the symptomatic manifestations of
22 Alzheimer's disease.
23 - - -
24 Q. Is that the same thing that we referred to as the
25 cholinergic deficit hypothesis?

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1 A. Yes. That's a shorthand for it.
2 Q. If you would look now on the right-hand column,
3 the bottom paragraph that begins, drugs that block
4 central acetylcholine. Muscarinic receptors have long
5 been known to disrupt higher cognitive function and induce
6 transient amnesic states.
7 - - -
8 A. Yes.
9 Q. What is the relationship of the drugs that block
10 muscarinic receptors to the cholinergic deficit hypothesis?
11 A. Well, those drugs are -- are able to induce
12 hypofunction, a component of cholinergic neurotransmission.
13 That is the muscarinic receptors. And so you can
14 pharmacologically induce low muscarinic receptor activity
15 and you can correlate it with these cognitive deficits.
16 Q. Was -- were the tests using these muscarinic
17 receptor blockers seen as supporting evidence for the
18 cholinergic deficit hypothesis?
19 A. Yes and no. Strictly speaking, the Drachman and
20 Leavitt paper reports to the memory problems that occur
21 in the aged and so as a strict model for -- for memory
22 impairment, has more to do with what occurs in the aged
23 than specifically with Alzheimer's disease.
24 Q. Was a connection drawn between aged memory problems
25 and Alzheimer's disease?

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1 A. Yes.
2 Q. And if you turn to the next page, the bottom -- the
3 last sentence in the paragraph that begins with the
4 discussion of muscarinic receptor blockers, the last
5 sentence reads, Thus, central cholinergic
6 neurotransmission may play a role in the processing of
7 recent memories and abnormalities of this system may
8 underlie some of the symptomatic manifestations of
9 Alzheimer's disease.
10 A. That's correct.
11 Q. What is the connection that you are drawing in your
12 article between the tests with muscarinic receptor
13 blockers and some of the symptomatic manifestations of
14 Alzheimer's disease?
15 A. Well, the -- the -- the centrally active muscarinic
16 antagonists cause impairments in recent or working memory,
17 and that is the type of memory impairment that is seen in
18 the early stages of Alzheimer's disease.
19 Q. Let me ask you now to turn to Tab 3 in your binder,
20 which is Plaintiffs' Exhibit 653, which I believe has
21 already been admitted into evidence.
22 A. Yes.
23 Q. Do you recognize Plaintiffs' Exhibit 653?
24 A. Yes. 653.
25 Q. What is this article?

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1 A. Yes, I do.

2 Q. And the first paragraph, do you see there's a

3 reference to some studies by Dr. Drachman and others

4 involving scopolamine induced memory deficits?

5 Do you see that?

6 A. Yes.

7 Q. Are those the Drachman studies that we heard about

8 over the last two days as forming these early foundations

9 in the cholinergic deficit hypothesis?

10 A. Yes. That is the case.

11 Q. Now, if you turn to the next paragraph, do you see

12 that there is a reference to followup studies? Do you

13 see that in the next paragraph, soon after the Drachman

14 study?

15 A. Yes.

16 Q. I wonder if you could read the first two sentences

17 into the record?

18 A. You mean -- beginning with Soon after?

19 Q. Beginning with Soon after.

20 A. Soon after the Drachman study, a series of papers

21 was published showing similarly parallel memory deficits

22 in aged monkeys and scopolamine-treated young monkeys.

23 In addition, scopolamine's age mimicking effects upon

24 memory were shown to be at least somewhat specific to

25 its effects on central muscarinic receptors, since

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1 similar age-like effects on memory were not obtained

2 with a number of other drug treatments, including

3 dopaminergic and alpha adrenergic blockers, several

4 nonspecific and catecholaminergic stimulants, nicotin

5 receptor blockers and peripheral anti-cholinergics.

6 Q. These studies, were they viewed as relevant to

7 drug development in the Alzheimer's field?

8 A. Yes.

9 Q. What was the relevance that was perceived of

10 these studies to Alzheimer's drug development?

11 A. They provided pharmacologic, we'll call them

12 pharmacologic targets. Where are you going to direct

13 your drug development and also directs you away from

14 where you're going to invest your time and effort.

15 So if you don't see effects with drugs that

16 interact with specific neurotransmitter systems or

17 receptors, you're unlikely to pursue that line of

18 investigation.

19 Q. Let me draw your attention to discussion that

20 similar age like effects on memory were not obtained

21 with nicotinic receptor blockers.

22 Do you see that?

23 A. Yes.

24 Q. What would that fact say to a person of ordinary

25 skill in the art in 1986 about the importance of

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1 nicotinic stimulation in the brain versus muscarinic?

2 A. Well, number one, they didn't see any effect.

3 Number two, at that time, it was very

4 unclear what nicotinic receptors were doing in the brain.

5 Q. And what would this series of studies, looking at

6 the different types of ages to find an age -- a memory

7 deficit, say to a person of skill in the art with regard

8 to prospects for a drug that was known to be a weak

9 muscarinic agent but to have nicotinic effects?

10 A. I think that would not encourage one to pursue

11 that drug.

12 Q. It would be discouraging?

13 A. Yes.

14 Q. Let me ask you to turn to Page 343.

15 A. Okay. I've got it.

16 - - -

17 Q. Do you see the section titled, current status of

18 treatment approach?

19 A. Yes, I do.

20 Q. Let me ask you. Dr. Bartus, was he a well-informed

21 scientist?

22 A. He was one of the leaders at the time.

23 Q. Would he have been aware of all these studies on

24 physostigmine that the defendants have been bringing to

25 the Court's attention?

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1 there will be so many other side effects that are
2 associated with the drug, because it interacts with these
3 other -- other cites and other functions, that the
4 treatment is simply intolerable.

5 So a treatment with too many side effects is
6 intolerable and therefore is not a treatment.

7 Q. Was, in the field in 1986, in attempting to develop
8 a method of treating Alzheimer's disease, were researchers
9 worried about side effects?

10 A. Yes, they were.

11 Q. Was one of the problems that was perceived that had
12 to be overcome to find a method of treating Alzheimer's
13 disease a problem with side effects?

14 A. Yes, it was.

15 Q. Was there perceived to be a problem as well with
16 finding a drug that could be tolerable for chronic use?

17 A. Yes.

18 Q. And is that the problem that Dr. Wurtman is
19 referring to in that sentence?

20 A. Yes. And I should point out that most of the
21 studies that were done were done with very short periods
22 of exposure. We're talking about a disorder that's
23 going to affect an individual for the rest of their
24 lives, not -- not minutes, not hours, not days, not
25 weeks, but years.

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1 Q. So would that make the problem with side effects
2 even worse?

3 A. Well, it certainly raises it to a higher level,
4 yes, of concern.

5 Q. Is Dr. Wurtman suggesting that physostigmine could
6 be used clinically in that sentence?

7 A. No.

8 Q. Is he saying the reverse, that physostigmine could not
9 be used clinically, in his view?

10 A. He's -- I think he's pointing out it's unlikely
11 physostigmine would be a tolerable treatment.

12 Q. And this problem with specificity, were -- were
13 there cholinesterase inhibitors that were known at the
14 time to be specific for that?

15 A. Well, there was -- I mean, there were cholinesterase
16 inhibitors that didn't get into the brain, so they were
17 selected for the periphery like neostigmine, which is
18 as Domino pointed out, quaternary amine. Its charge
19 doesn't get into the brain.

20 There were others that get in the brain and
21 it had to do with relative distribution between the brain
22 and the periphery.

23 Q. And was galanthamine at the time thought to be
24 specific for the brain and to focus on the brain?

25 A. Well, I think most of the studies -- it's not even

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1 studies. Most of the reports from that middle European
2 literature on galanthamine used it as treating disorders
3 of the neuromuscular junction, like myasthenia gravis,
4 or to terminate the polarizing effect of anesthetic
5 agents at the neuromuscular junction. I mean, most of
6 it was pointing towards the periphery.

7 Q. So would the concern that Dr. Wurtman identified
8 with specificity, would that appear to a person of
9 ordinary skill in the art in 1986 to apply to galanthamine
10 as well?

11 A. Well, that would be specificity pointed in the wrong
12 direction.

13 Q. So galanthamine would appear to be moving in the
14 wrong direction?

15 A. Right.

16 Q. Let me ask you to turn your attention to the next
17 page, to the sentence right before Item 5, that begins,
18 similar arguments can be adduced.

19 A. I'm just -- I'm trying to get myself oriented here.

20 In the middle? Oh. Yes. Excuse me.

21 Similar arguments can be adduced for the
22 wisdom of providing a supplemental source of choline to
23 patients receiving acetylcholinesterase inhibitors like
24 physostigmine. These drugs, by slowing the hydrolysis
25 of intra-synaptic acetylcholine, diminish the amount

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1 of free choline available for re-uptake into the
2 terminal and for acetylation back to acetylcholine.

3 Q. What is he saying about the possible effects of
4 cholinesterase inhibitors in that sentence?

5 A. When acetylcholinesterase is released, it's
6 broken down, after it hits the receptors, broken down.
7 The cholinergic neurons have a transporter to bring
8 the choline back in so it can be recycled to make more
9 acetylcholinesterase. It's incredibly high. And if

10 the acetylcholinesterase isn't hydrolyzed so it
11 diffuses away, then the cholinergic terminal actually
12 becomes deficient in choline to make more
13 acetylcholinesterase and this would cause it to
14 cannibalize its own membranes that generate choline.

15 So the concern he was raising was the
16 cholinesterase inhibitors, while they may inhibit the
17 function of acetylcholinesterase, could theoretically
18 lead to further degeneration of cholinergic neurons.

19 Q. Was there a concern in 1985 that cholinesterase
20 inhibitors by -- could reduce the available
21 acetylcholinesterase to be released back into the
22 synapse?

23 A. Well, it could interfere with the regeneration of
24 acetylcholinesterase by preventing the hydrolysis in
25 the synapse and, as I said, could also lead to

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1 cannibalization of the cholinergic terminal.

2 Q. How would that concern relate if one in instead

3 used a highly specific M-1 agonist?

4 A. Well, it leaps over the hurdle. It doesn't depend

5 on pre-synaptic cholinergic activity. It does not even

6 depend on pre-synaptic cholinergic activity which we

7 know is impaired in the disorder.

8 Q. Would the concerns like those expressed by Dr.

9 Wurtman lead one in the direction that the defendants'

10 expert, Dr. Levey, went in towards highly specific

11 muscarinic agonists?

12 A. Yeah. That turned out to be a major target for

13 many of the pharmaceutical companies.

14 Q. Has any highly specific muscarinic agonist succeeded

15 as a treatment for Alzheimer's disease?

16 A. Not that I'm aware of. We actually tried one of

17 them in the Leechin model, which is oxotremorin and

18 unfortunately causes the grossest thing I've ever

19 seen, bloody tears, so we just got out of that.

20 Q. But, to your knowledge, there are no --

21 A. No.

22 Q. And have any muscarinic agonists yet succeeded

23 as a treatment for Alzheimer's?

24 A. Not that I'm aware of.

25 Q. Let me direct your attention to Tab 7, which you

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1 will recognize is the '318 patent.

2 A. Okay.

3 Q. If you will turn to Column 2 of the patent,

4 beginning at Line 45...

5 A. Okay. Column 2, Line 45. The following test.

6 Q. Yes.

7 A. Do you want me to read that?

8 Q. Well, it might be useful to read at least the first

9 sentence.

10 A. Okay. The following test provides a good animal

11 model for Alzheimer's disease in humans. A select lesion

12 is placed in a subcortical nucleus, known as the nucleus

13 basalis of Meynert, with a resultant cortical cholinergic

14 deficiency, similar in magnitude to that seen in early

15 to moderate stage Alzheimer's disease.

16 - - -

17 Q. Did you do any work relating to that model?

18 A. We developed it.

19 Q. Let me ask you first before we get to your work

20 with galanthamine.

21 How did that model, selective lesion model,

22 compare to the scopolamine model in terms of modeling

23 Alzheimer's disease?

24 A. Scopolamine is a drug that blocks muscarinic receptor.

25 - - -

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1

2 A. (Continuing) It has nothing to do with the

3 functional integrity, functional integrity of cholinergic

4 neurons. Rapidly reversible. Disappears when the drug

5 is metabolized.

6 Alzheimer's disease is a disorder of

7 degeneration of cholinergic neurons, among others but,

8 in particular, cholinergic neurons and nucleus basalis.

9 This lesion causes that degeneration and that pathology

10 was identified in the nucleus basalis in individuals

11 who died with Alzheimer's disease as a consequence of

12 that lesion.

13 We went across the street, to see Don Price,

14 Head of Neuropathology, let's look at the brains of

15 individuals who died of Alzheimer's disease, and on the

16 basis of this lesion, we were able to show they had the

17 same lesion.

18 So this is mimicking the structural loss of

19 cholinergic neurons in Alzheimer's disease and therefore

20 it does three things. Number one, it reduces the number

21 of cholinergic terminals, which is the real-life

22 situation in Alzheimer's disease.

23 Number two, it exposes the muscarinic

24 receptors.

25 Number three, it exposes the nicotinic

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1 receptors.

2 Q. So we've heard testimony before that the scopolamine

3 model was focused on the muscarinic system. Does this

4 selective lesion model have the same focus on the

5 muscarinic system?

6 A. No. It -- it allows you to determine what happens

7 when you lose cholinergic terminals, what happens to

8 nicotinic receptors, what happens to muscarinic receptors.

9 Q. Did you carry out any work with galanthamine using

10 the model that is set forth in the '318 patent?

11 A. Yes, I did.

12 Q. And how did it come about that you did that work?

13 A. As I started telling you before, but I will go back.

14 In the late spring, early summer of 1986, I got a call

15 from Bonnie Davis, and she said that she had a very

16 interesting drug and a potential treatment for Alzheimer's

17 disease.

18 And as I can recall, she said the drug was --

19 had already been in humans, it was tolerable, and it had

20 the peculiar effect where it looks like it enhanced

21 nicotinic receptors.

22 A couple of things to put in context. Number

23 one, at that time, there was no treatment for Alzheimer's

24 disease and, having worked on this model and being very

25 interested in the area and the human toll it causes,

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1 this sounded very intriguing.
 2 Number two, she didn't know this, but we had
 3 actually just finished a study looking at nicotinic
 4 receptors in the brains of individuals that died with
 5 Alzheimer's disease, with Peter Whitehouse. And what
 6 we found, that unlike muscarinic receptors, which appeared
 7 to be spared, there was substantial losses in nicotinic
 8 receptors in the cortex of hippocampus. And this had
 9 never been shown before.
 10 So I don't take up research projects lightly
 11 in my lab. I had a stellar student coming and I thought,
 12 aha, this could be very interesting. We'll take a look.
 13 Q. And who was that stellar student?
 14 A. Joann Sweeney, now Joann Berger Sweeney, who's
 15 the Associate Dean at Wellesley College.
 16 Q. That work you talked about with the nicotinic
 17 receptor that you did with Professor Whitehouse, was
 18 that published before January of 1986?
 19 A. No. No. It was -- it was published later in '86.
 20 Q. When Dr. Bonnie Davis approached you and asked
 21 you to carry out some animal tests on galanthamine, did
 22 you think that her proposal was simply a guess?
 23 A. No. I mean, the -- her neuroendocrine signal was
 24 intriguing to me. There were a number of things that
 25 were intriguing. The neuroendocrine was intriguing.

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1 And acetylcholine seemed to be intriguing, given what was
 2 going on with physostigmine and tacrine.
 3 Q. Did her proposal seem to you scientifically well
 4 grounded?
 5 A. The rationale was well grounded and -- and it fit
 6 in very nicely with the lesion model because that was
 7 the model where you could really see if there was a
 8 contribution of nicotinic receptors to -- you know, to
 9 the effects of acetylcholinesterase inhibitors.
 10 Q. Did you think at the time it was obvious to use
 11 galanthamine as a treatment for Alzheimer's disease?
 12 A. I wish I had thought of it.
 13 Q. Do you tend to do obvious science in your lab?
 14 A. No. And this became Joann Sweeney's thesis
 15 project, thesis projects at Hopkins. We have a
 16 committee that oversees them, that reviews them. If --
 17 if somebody came in with an obvious research question,
 18 they would go back to the drawing boards and come up
 19 with something better, and their mentor would look
 20 rather silly. So this was not obvious.
 21 Q. And I take it Dr. Berger Sweeney did, in fact,
 22 get her Ph.D. and move on in her career?
 23 A. Yes. She has been -- she has been very successful.
 24 Q. Let me --
 25 A. Continues to collaborate with me.

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1 Q. Let me ask you to turn to tab eight, Plaintiffs'
 2 Exhibit 1308.
 3 A. Okay.
 4 Q. Would you identify Plaintiffs' Exhibit 1308 for
 5 the record?
 6 A. Yes. This is a -- an abstract that we prepared
 7 for a presentation to be given at the society, the
 8 annual meeting of the Society for Neuroscience. The
 9 Society for Neuroscience is -- is the, capital T-H-E,
 10 meeting in neuroscience in the world. About this time
 11 20,000 members, now 40,000, and where you want to show
 12 your research.
 13 Q. And is this an abstract that was prepared in the
 14 course of your conducting research at Hopkins?
 15 A. Yes. This was the first report of our studies with
 16 galanthamine in the lesion model.
 17 Let me just say two things about our work.
 18 We had never done behavioral work in our laboratory. We
 19 had collaborated with Dave Olten in rats, and so we had
 20 Joanne Sweeney come in. We had to set this whole thing
 21 up de novo, and we also had to demonstrate our bona fides
 22 as a report from a laboratory that had not been generally
 23 known for doing behavior.
 24 So the report is really extremely detailed
 25 for a -- the abstract is extremely detailed for an

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1 abstract citing neuroscience, where you typically, you
 2 know, publish one or two facts.
 3 Q. And is the abstract archived so that it can be
 4 referred to by people working in the field?
 5 A. Yes, absolutely. This is where you plant the flag
 6 scientifically, so to speak, because it's archived,
 7 meaning it's in the libraries and people can cite it.
 8 You can set precedence with it.
 9 MR. SIPES: I would move into evidence
 10 Plaintiffs' Exhibit 1308.
 11 MR. GRACEY: No objection.
 12 *** (Plaintiffs' Exhibit No. 1308 was received into
 13 evidence.)
 14 MR. SIPES: Would you pull that up now?
 15 BY MR. SIPES:
 16 Q. Let me draw your attention to the first paragraph.
 17 A. Yes.
 18 Q. The last sentence reads GHB. That's galanthamine
 19 hydrobromide?
 20 A. Yes.
 21 Q. GHB has an in vivo half-life of approximately six
 22 hours, making its effects longer than most previously
 23 tested acetylcholinesterase inhibitors.
 24 Do you see that?
 25 A. Yes.

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1 1986.
 2 Q. Well, I note there's one article, Thornton and
 3 Gershon, 1986. What is that article?
 4 A. Which one?
 5 Q. Is that a review article?
 6 A. Yes.
 7 Q. All the information in the chart, is that
 8 information that would have been known to a person of
 9 ordinary skill in the art in 1986?
 10 A. In 1986.
 11 Q. Is that a yes?
 12 A. Yes.
 13 Q. Will you take me through the chart, tell me what
 14 the chart shows?
 15 A. What I tried to do is a comparison among
 16 galanthamine, physostigmine and tacrine, and as of 1986,
 17 as far as I know, physostigmine and tacrine were
 18 the two acetylcholinesterase that had been looked at
 19 most closely in Alzheimer's disease and in some people's
 20 minds might ultimately be the basis for treatment.
 21 And so I'm just looking at the
 22 characteristics.
 23 So if you look at potency, and generally in
 24 drug development, we tend to want to have drugs that are
 25 more potent than less potent. And I -- Dr. Domino gave

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1 an excellent discussion of efficacy. Efficacy is very
 2 important, but the less potent a drug is, the more
 3 likely -- that means you have to use more of it, you
 4 know. 50 milligrams versus two grams, and the more of it
 5 you have to use, the greater likelihood that the drug is
 6 going to interact with some other processes and cause
 7 side effects.
 8 So potency is generally conceived as being
 9 positive.
 10 So galanthamine, from the literature we know,
 11 is a relatively weak acetylcholinesterase inhibitor,
 12 much weaker than physostigmine and much weaker than
 13 tacrine.
 14 Receptor specificity. So if you inhibit
 15 acetylcholinesterase, you increase acetylcholinesterase
 16 levels, and one would suspect that since that's
 17 pre-synaptic, you shouldn't see any post-synaptic
 18 receptor specificity. So physostigmine and tacrine
 19 should enhance acetylcholine at both -- both at nicotinic
 20 and muscarinic receptors.
 21 Oddly enough, what comes up in the literature
 22 with galanthamine is it's described as weekly muscarinic
 23 in terms of its side effect profile in those series of
 24 Middle Eastern studies discussing its use. And, in
 25 addition, it -- it appears to be more nicotinic because

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1 it was used primarily for treating issues around the
 2 nicotinic neuromuscular junction. And Bonnie's findings
 3 suggest that it had central nicotinic effects.
 4 Some say inhibition of butyrylcholinesterase
 5 in addition to acetylcholinesterase will give you more
 6 bang for your buck. Other people have concerns that
 7 inhibiting both of them may allow acetylcholine to diffuse
 8 so broadly that it would increase side effects. I should
 9 point out Rivastigmine is a butyrylcholinesterase
 10 inhibitor and appears to have more side effects.
 11 Galanthamine select for acetylcholinesterase
 12 whereas physostigmine and tacrine inhibit both
 13 acetylcholinesterase and butyrylcholinesterase mechanism.
 14 The acetylcholine binds to a site on the
 15 enzyme where it's broken down. A competitive inhibitor
 16 would bind to that same site and compete against
 17 acetylcholine. And the advantage of that is that the
 18 higher the concentration of acetylcholine you get, then
 19 the lesser inhibition one would see with the competitor,
 20 which may dampen potential side effects.
 21 So galanthamine is competitive. I see that
 22 as good. Physostigmine is competitive. Well, that's one
 23 good aspect of physostigmine. Tacrine is not competitive,
 24 which means it inhibits the enzyme regardless of how much
 25 acetylcholine is there.

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1 Duration of action. Now, reading -- my
 2 reading of the literature is that -- that it was
 3 perceived that galanthamine was relatively short-acting.
 4 Not a good thing if you want to use it clinically to
 5 treat a chronic disorder.
 6 Clearly, physostigmine has very short action.
 7 At best, two hours. And that's why ultimately people
 8 try to develop slow release physostigmine, so they can
 9 have it hang around long enough. You don't want to be --
 10 especially if you are demented and your memory is
 11 impaired. You don't want to be on a regimen that
 12 requires taking drugs every four hours.
 13 And the tacrine had the advantage of being
 14 long-acting.
 15 What was the agent used for -- you know, what
 16 was it used for? So galanthamine, looking at the
 17 literature, was primarily used for disorders of the
 18 peripheral nicotinic cholinergic system perceived to have
 19 weak muscarinic effects. It had some central effects,
 20 but that was not a major focus.
 21 Physostigmine was clearly seen as a
 22 centrally active acetylcholinesterase inhibitor as was
 23 tacrine, which would be good if you want to develop
 24 drugs for treating Alzheimer's disease.
 25 So in sum, in terms of the treatment for

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1 Alzheimer's disease, clearly, you'd want to look at
 2 tacrine very seriously except for what it does to the
 3 liver.
 4 Physostigmine could be a contender except for
 5 its very short duration of action and a lot of its side
 6 effects.
 7 And I would think galanthamine would not be
 8 on anyone's list who was, as they say, skilled in the
 9 art.
 10 Q. Let me try to go by that one by one. In terms of
 11 the perspective now of a person of ordinary skill in the
 12 art in 1986, what would the weak potency of galanthamine
 13 tell the person of ordinary skill in the art in 1986
 14 with regard to galanthamine's prospects as a treatment
 15 for Alzheimer's disease?
 16 A. That would -- it would be a poor prospect.
 17 Q. And why would it appear to be a poor prospect?
 18 A. Because, generally, the weaker the drug, the lesser
 19 the specificity.
 20 Q. Now let's go to receptor specificity.
 21 What would a person of ordinary skill in the
 22 art in 1986 make of the fact that galanthamine appeared
 23 to have pronounced nicotinic effects and was described
 24 as a weak muscarinic agent?
 25 A. Well, two things one that's somewhat surprising.

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1 But the second thing is that, as we -- as we
 2 saw looking at the work of Bartus among many others and
 3 where the industry went, they went towards drugs that
 4 would have muscarinic effects because of the scopolamine
 5 model and preferably directly activate muscarinic
 6 receptors.
 7 Q. Now, let me come to the next one. Enzyme
 8 specificity. You receive to both acetylcholinesterase
 9 and is it butryl --
 10 A. It's an artificial substrate they use.
 11 Acetylcholinesterase can't metabolize. It's a way for
 12 measuring the other enzyme.
 13 Q. So butyrylcholinesterase. Did you refer to it as
 14 pseudo cholinesterase?
 15 A. Yes.
 16 Q. In Alzheimer's patients, what was known about
 17 levels of acetylcholinesterase in Alzheimer's patients
 18 in 1986?
 19 A. Well, acetylcholinesterase is in part located on
 20 the cholinergic neurons and the levels fall in Alzheimer's
 21 disease.
 22 Q. And what was known about the levels of butryl
 23 cholinesterase in Alzheimer's patients in 1986?
 24 A. I think the activity went up, to my recollection.
 25 Q. So what would a person of ordinary skill in the

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1 art in 1986 think about the prospects of galanthamine
 2 as a treatment for Alzheimer's disease given the fact
 3 that it did not inhibit butryl cholinesterase?
 4 A. Well, back in 1986, I did make some comments
 5 about specificity, but I think back in 1986, one would
 6 be -- one could be interested in the possibility that
 7 hitting butryl cholinesterase may give you more bang
 8 for the buck.
 9 Q. So an inability to inhibit butryl cholinesterase
 10 in 1986 could seem discouraging?
 11 A. It could be, yes.
 12 Q. What would be thought about the inability to
 13 inhibit butryl cholinesterase today? Have we learned
 14 more about butryl cholinesterase?
 15 A. Yes. As I said, Rivastigmine is one of the --
 16 one of the three acetylcholinesterase inhibitors out
 17 there to treat Alzheimer's disease. It's the one that's
 18 pretty effective at butyrylcholinesterase and, as Dr.
 19 Levey pointed out, that makes it his third choice,
 20 because of the side effect profile, presumably related
 21 to butyrylcholinesterase, but, you know.
 22 Q. And so today, has -- is the fact that galanthamine
 23 does inhibit butyrylcholinesterase, is that an advantage
 24 of galanthamine?
 25 A. Today, it is.

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1 Q. And I think you've probably gone over the rest of
 2 them. Let me just take the -- following the principal
 3 prior therapeutic use. The use of galanthamine was
 4 peripheral, what would that tell a person of ordinary
 5 skill in the art in 1986 about the prospects for
 6 galanthamine?
 7 A. Well, obviously, Alzheimer's disease is a disease
 8 of central cholinergic neurons and as a drug that
 9 works -- is perceived to work primarily in the periphery
 10 would not -- not be an attractive candidate.
 11 Q. Let me ask you to look at a few of the exhibits
 12 that have been discussed by defendants' experts and I
 13 believe at Tab 23 --
 14 A. Just a second.
 15 Q. -- you'll find Plaintiffs' Exhibit 1181.
 16 A. Tab 23? I've got nothing in 23.
 17 (Pause.)
 18 BY MR. SIPES:
 19 Q. Why don't we pick up another topic while we're
 20 trying to sort through the confusion there. Then we can
 21 come back to that.
 22 Let me ask you, you mentioned the somewhat
 23 surprising fact that -- that galanthamine has pronounced
 24 nicotinic effects and is weak muscarinic.
 25 Do you have an understanding now of why that

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1 is?

2 A. Not really.

3 Q. Is there any mechanism for galanthamine that might
4 explain why it would have more nicotinic than muscarinic
5 effect?

6 A. Oh, sorry. I had a little TIA there.

7 Actually, yes. I'm sorry.

8 Galanthamine has been shown to be a positive
9 allosteric modulator of nicotinic receptors.

10 Q. Could you explain what that means?

11 A. Yes. So there's -- there is a site on the
12 nicotinic receptors to which galanthamine binds and when
13 it binds to that site, it makes the receptors much more
14 responsive to acetylcholine. There's clear precedence
15 for this in pharmacology. Benzodiazepines, for example,
16 which are anti-anxiety agents, bind together receptors
17 and enhance their response together. That's a mechanism
18 that has been known for 25 years.

19 This mechanism of galanthamine was discovered
20 in the late 1990's by Edison Albuquerque (phonetic).

21 Q. Was it known in 1986 that galanthamine was a
22 modulator of the nicotinic receptor?

23 A. No.

24 Q. Was it suspected that it would be a modulator --

25 A. No. What I would say that Dr. Davis' finding with

1
2 A. (Continuing) And that suggests that there is some
3 additional mechanism of action of galanthamine that can
4 account for this equal efficacy.
5 So this is inferred to be clinically
6 meaningful. I would say it's very difficult to determine
7 unequivocally that that -- that's the case. But there is
8 no question that galanthamine is an allosteric modulator
9 of nicotinic receptors.
10 Does that answer your question?
11 Q. I believe so.
12 Let me try to break that down by starting with
13 the abstract. So let's look at the abstract of the art,
14 if we could. Galanthamine is a rather weak
15 acetylcholinesterase inhibitor currently approved for
16 the symptomatic treatment of Alzheimer's disease, with
17 possible additional allosteric potentiating effects at
18 the nicotine ACH receptor.
19 Do you see that?
20 A. Yes.
21 Q. Early data from in vitro biochemical tests suggest
22 that donepezil --
23 A. Yes.
24 Q. Is this correct galanthamine is a rather weak
25 cholinesterase inhibitor?

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1 A. Yes. We just discussed that.
2 Q. So the prior art was right there. Galanthamine is
3 not very potent; is that correct?
4 A. That is correct.
5 Q. Is this article an attempt to understand, then,
6 how galanthamine can have therapeutic effects despite
7 its lack of potency?
8 A. Well, this gets us back to Dr. Domino. Potency
9 and efficacy. And what they are pointing out is that
10 it's efficacious at less acetylcholinesterase than --
11 it's not a matter of being weak. It's that you can get
12 the same response with less acetylcholinesterase. And
13 so the question is: How can that be? It's got to have
14 another action.
15 And, you know, the most parsimonious thing
16 in terms of thinking about cholinergic function is the
17 nicotinic, allosteric modulate modulating effect.
18 Q. Let's turn now to the very last page of text of
19 the article and to the last paragraph of the summary.
20 Do you see that the last two sentences --
21 could you read the last two sentences, beginning with
22 If in --
23 A. Yes. If in such studies, both compounds have
24 the same in vivo effect, this argues strongly for an
25 additional mechanism of action for galanthamine to

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1 make up for the difference in acetylcholinesterase
2 inhibition. Allosteric modulation of nicotine ACH
3 receptors by galanthamine is a prime candidate for this
4 effect.
5 Q. The two compounds that are being talked about
6 there, do you know what they are? Is that galanthamine
7 and donepezil?
8 A. Yes.
9 Q. What are they proposing for galanthamine as opposed
10 to donepezil?
11 A. Galanthamine has an allosteric effect and donepezil
12 does not.
13 Q. Are they proposing this is compensating for the
14 weak cholinesterase inhibition in order to give similar
15 type effects to donepezil?
16 A. There's a little more implicated in there. It
17 points to a more potent nicotinic effect. Remember
18 when I had my little TIA and you said what's different
19 and that is that when you look at the pharmacology in
20 the old -- in the older studies, it comes up looking
21 much more nicotinic and less muscarinic and how can
22 that be if you're inhibiting acetylcholinesterase that
23 should not differentiate between the two receptors, and
24 I think this provides an explanation.
25 Q. And the explanation is allosteric modulation of

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1 the nicotinic receptor?
2 A. Yes.
3 Q. Do you believe that it's a scientifically reasonable
4 conclusion that allosteric modulation of the nicotinic
5 receptor is responsible for at least part of the
6 therapeutic effects of galanthamine?
7 A. I think it's a reasonable scientific inference, yes.
8 Q. Do you think it is the best inference in light of
9 all the data?
10 A. It certainly is consistent with how it works at a
11 molecular level and how it behaves in vivo.
12 Q. And the authors refer to it as the prime candidate
13 for the explanation.
14 Would you agree with their conclusion?
15 A. Yes.
16 Q. Let me ask you to turn to Tab 12.
17 A. What was that last --
18 Q. Tab 12.
19 A. Just a second. Tab 12.
20 Q. And --
21 MR. SIPES: Your Honor, I note it's almost
22 12:14. I could get started on this document, if you'd
23 like, or we could take --
24 THE COURT: Well, we started at 10:20, so if
25 you want to go to 12:20...

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1 Q. Do you agree that there is scientific evidence for
2 that statement?

3 A. Yes. Actually, I wrote a review article that
4 reviewed this and other studies, I think published in
5 2001, looking at potential course-altering effects of
6 galanthamine.

7 Q. And what is your conclusion about the best
8 scientific understanding of whether or not galanthamine
9 has an effect on the progression of Alzheimer's disease?

10 A. Well, in our review, there was actually two things
11 that were seen.

12 One is what Murray found in his study on
13 patients continuously, on galanthamine over 36 months,
14 where the -- the rate of decline slowed in patients on
15 galanthamine versus historical placebo controls.

16 The second is the results of studies that
17 show if you have bad patients and you put one on a
18 placebo arm and the other on a galanthamine arm and you
19 take them out I think it's to a year, I can check the
20 paper, and then the ones that are on the placebo arm go
21 on to galanthamine, they do not go up to the levels of
22 cognitive improvement that are seen with the individuals
23 that were continuously on galanthamine.

24 So that also suggests that being on the drug
25 somehow alters the course of the disease. And, now, I'm

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1 not -- I'm not a geriatrician, but it is my impression
2 that this is encouraging people to treat early as
3 opposed to delaying treatment.

4 Q. And why would that encourage people to treat early
5 rather than delaying patients?

6 A. Well, if you have a course altering effect, as I
7 just said, if you compare the ones that aren't treated
8 for a year to the ones that are treated for a year,
9 when you put the untreated ones on, they don't go up
10 to the level that the ones that are being continuously
11 treated.

12 So it looks -- it looks as if not being
13 treated results in further deterioration.

14 If I could say parenthetically, in the area
15 of schizophrenia, it turns out the longer you don't
16 treat psychosis, the worse the outcome is when you start
17 treating it. So I think these disorders are bad for
18 your brain.

19 Q. And if the disorders are bad for the brain, then
20 treating the disorder could, in fact, prevent the brain
21 from getting worse faster?

22 A. Well, again, these treatments are considered
23 symptomatic. They are just dealing with a deficiency
24 of a neurotransmitter. Acetylcholine in this case.

25 But I think we have to recall that

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1 neurotransmitters are not simply messengers in the brain
2 for information processing. They do a whole variety of
3 other things. And especially acetylcholine through
4 nicotinic receptors can have trophic effects on neurons
5 and can alter the processing of this APP to generate A
6 beta.

7 So, you know, there's -- there are actions
8 that have been demonstrated in the test tube, in the
9 Petri dish with acetylcholinesterase inhibitors, among
10 them galanthamine, that suggest potential mechanisms
11 for course-altering effects.

12 So they may not only affect cognition, they
13 may indirectly affect some fundamental aspects of the
14 disorder.

15 Q. And if we turn to page -- go to the next column,
16 you'll see the paragraph that begins, Enhancement of
17 cholinergic neurotransmission might slow progression
18 in AD patients by several possible mechanisms.

19 Do you see that?

20 A. Yes.

21 Q. Is this proposing some neurochemical mechanisms by
22 which galanthamine might slow the progression of
23 Alzheimer's disease?

24 A. Took the words right out of my mouth, yes.

25 Q. And could you explain what the proposed mechanisms

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1 are?

2 A. Okay. So working through muscarinic receptors,
3 and can favor the processing of this protein APP, amyloid
4 precursor protein, in a way that directs it against
5 making A beta, the bad protein. It can affect
6 phosphorylation of these tau proteins that contribute to
7 the formation of neurofibrillary tangles.

8 As I mentioned, there's evidence that
9 activation in nicotinic receptors can have
10 neuroprotective effects. They can make neurons less
11 sensitive to the toxic effects of A beta.

12 So there's a number of different mechanisms
13 that could come into play that, through which enhancement
14 of cholinergic neurotransmission and, more specifically,
15 nicotinic neurotransmission could have disease-altering
16 effects.

17 Q. Do you think the neurochemical mechanisms that are
18 proposed for galanthamine to slow disease progression,
19 are those scientifically reasonable?

20 A. I think they're plausible, yes.

21 Q. Have they been endorsed by experts in the field?

22 A. Yes.

23 Q. And is it correct that this slowing disease
24 progression has never been proved by a double-blind
25 clinical trial?

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1 A. Well, it's -- it's -- it's very difficult, if
2 not impossible, to do at the present time, from my
3 perspective, because no one would ethically put
4 individuals with Alzheimer's disease on a placebo for
5 three years now to see if they -- if they lose their
6 nerves faster than those that get treatment.

7 That's the problem you really face in terms
8 of asking some of these very important, but difficult
9 questions now that we have treatments.

10 Q. So could -- is it ethically possible to prove
11 this slowing of disease progression through the sort
12 of double-blind studies that we use for FDA to prove
13 the effects of drugs?

14 A. Again, repeat -- I'm repeating myself. No, I
15 don't think it's ethically feasible to do that now
16 that we have treatments.

17 There may be ethical reasons for doing
18 short placebo controlled trials, but the type of trial
19 that would really demonstrate disease altering effects
20 would be -- would require non-treatment for way too
21 long.

22 Q. But do you believe the proposal that galanthamine
23 slows the progression has been accepted by treating
24 physicians enough that they now move to treat patients
25 as soon as possible?

1 blood/brain barrier isn't working.

2 Q. Might that be, for example, cases of local brain
3 damage?

4 A. That would be a case of say tumor, local brain
5 damage from trauma.

6 - - -

7 Q. Would a person of ordinary skill in the art believe
8 it a reasonable reading of a scientific article to read
9 it as suggesting neostigmine as treatment for Alzheimer's
10 disease?

11 A. You could read this in two ways. You could read it
12 and say that it played in the central activity of
13 acetylcholinesterase with acetylcholinesterase inhibitors
14 and that he doesn't know what he's talking about.

15 - - -

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1
2 A. (Continuing) So he doesn't know what he's talking
3 about. Or you could read it in the other way in terms
4 of his reference to Luria, which means he's talking
5 about traumatic brain injury, which has nothing to do
6 with Alzheimer's disease.

7 MR. SIPES: I believe I have no further
8 questions.

9 THE COURT: Cross-examination.

10 CROSS-EXAMINATION

11 BY MR. GRACEY:

12 Q. Good afternoon, Dr. Coyle.

13 A. Good afternoon.

14 Q. As you may recall, my name is Taras Gracey of
15 Winston and Strawn.

16 A. Yes.

17 Q. Here on behalf of Barr Labs.

18 Dr. Coyle, would you agree, or are you willing
19 to state here today in open court, that to a reasonable
20 degree of scientific certainty, the nicotinic allosteric
21 modulator has a proven clinically meaningful benefit?

22 A. I think what I said is a reasonable scientific
23 inference that the allosteric modulatory effect of
24 galanthamine could contribute to its therapeutic effect.

25 Q. I appreciate, Doctor, but I'd like you to answer

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1 shown, to use your words, proof of principle, and yet
2 you're saying that knowing all of that and knowing all
3 about galanthamine, also being in the same class,
4 being safe, being used in humans, being a cholinesterase
5 inhibitor, you're standing here today or sitting here
6 today and willing to state it wouldn't have been obvious
7 to at least try?

8 A. I'm saying it wouldn't be obvious in terms of what
9 was going on over here. It was not -- that is in the
10 United States. And the -- in the research community, I
11 don't think galanthamine was on the horizon anywhere,
12 so that's another reason it's less likely to be used.

13 But, again, as a scientist, you would look
14 at what are the properties you would want, and when I
15 look at the literature on galanthamine, ignoring what
16 Dr. Davis saw there, from her neuroendocrine perspective,
17 I would say galanthamine would not be very high on the
18 list. I think it would be very low down the list of
19 drugs to look at in Alzheimer's disease.

20 Q. And yet you did the animal model?

21 A. I did the animal model for two reasons.

22 Number one, she said this drug -- well,
23 three reasons.

24 Number one, she said, I have identified a
25 drug that is tolerable in man and I knew the literature

1 and very modest muscarinic receptor side effects.

2 Q. Well, let's talk a little bit about the muscarinic
3 and nicotinic receptors, but let me first ask you this:
4 You, on your chart here, you have galanthamine as a
5 weak inhibition of acetylcholinesterase; is that right?

6 A. I would say relatively -- it's relatively weak
7 vis-a-vis physostigmine and tacrine.

8 Q. Now, this is under the term potency; right?

9 A. Yes.

10 Q. And you heard Dr. Domino yesterday say that when
11 you have a weak inhibitor of acetylcholinesterase, you
12 give a higher dose. That's it. It's got nothing to
13 do with efficacy; isn't that right?

14 A. I answered that question before. I said there are
15 two issues here. One is potency and one is efficacy and
16 the lower the potency, the higher dose of an agent you
17 have to give, and that raises the risk that that agent
18 is going to interact with other things that cause side
19 effects.

20 So generally, in drug development, one
21 likes to go for increased potency to lower the risk of
22 secondary adverse interactions.

23 Q. You know what the therapeutic window for
24 galanthamine was? It was quite large, wasn't it?

25 A. On experimental animals it was maybe like

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1 on physostigmine and tacrine for treatment of
2 Alzheimer's disease, and there was no treatment. Sounds
3 good to me.

4 The second thing she said was it has this
5 very unusual property of -- of acting at nicotinic
6 receptors, enhancing nicotinic receptor function.

7 Number three, I had just -- I had just got
8 done with a study with Peter Whitehouse for the first
9 time showing there was striking reductions in nicotinic
10 receptors. The first time that was demonstrated as
11 far as I know.

12 And that was in the face of normal muscarinic
13 receptors.

14 So as I said, we don't do trivial experiments.
15 We don't do obvious experiments. This seemed to me --
16 she had a proposal that connected the dots that raised
17 very interesting questions and worth the effort to check
18 it out in a model in which there is degeneration of
19 cholinergic neurons in both nicotinic and muscarinic
20 receptors would come into play.

21 Q. And the dots she connected, galanthamine, safe,
22 humans will tolerate it, cholinesterase inhibitors;
23 right?

24 A. Galanthamine in humans safe and well tolerated.
25 Cholinesterase inhibitor, selective nicotinic effects,

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- 1 Q. Would a person of ordinary skill in the art
- 2 understand galanthamine to be necessarily related to
- 3 palagra in reading this?
- 4 A. It would be confusing.
- 5 Q. Is Alzheimer's disease one of the key words in this
- 6 index?
- 7 A. No.
- 8 Q. Is senile dementia of the Alzheimer's type mentioned
- 9 there?
- 10 A. No.
- 11 Q. Now, I gather that reference at 2358, that's the
- 12 jump to the abstract from Excerpta Medica?
- 13 A. Yes.
- 14 Q. Let's take a look at that.
- 15 A. I did.
- 16 Q. Second page of the exhibit, medical management of
- 17 Bhasker.
- 18 Do you see that?
- 19 A. Yes.
- 20 Q. In the abstract, is there a reference to
- 21 galanthamine at all?
- 22 A. There is no reference to galanthamine.
- 23 Q. Is there a reference to deinhibition?
- 24 A. No.
- 25 Q. The is there a reference to restoration of

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- 1 cortical function?
- 2 A. I don't think so.
- 3 Q. Or to be clear, is there any reference to
- 4 restoration of higher cortical function?
- 5 A. Not that I'm aware of.
- 6 - - -
- 7 Q. Is there a reference to progressive dementia?
- 8 A. Let me see. I read this in before.
- 9 With regard to progressive dementia, there
- 10 appears to be very little to offer, only management, no
- 11 treatment is possible.
- 12 Q. Would a person of ordinary skill in the art
- 13 searching for a treatment for Alzheimer's disease who
- 14 read the Excerpta Medica abstract, would he or she think
- 15 to look in Bhasker for a treatment for Alzheimer's
- 16 disease?
- 17 - - -
- 18
- 19
- 20
- 21
- 22
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- 25

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1 Q. From a scientific perspective, do you believe that
2 the best interpretation of the evidence we have so far
3 is that the allosteric modulation of the nicotinic
4 receptor does have clinical benefit?

5 A. That's what I was saying. Some of the scientific
6 evidence supports this, this inference. It's not --
7 there's not a lot of contradictory stuff out there.
8 It's pretty linear and a -- and it's supported at a
9 molecular level. It's supported at an enzymatic level
10 and it's supported at a behavioral level.

11 Q. Let me ask you a few questions about potency.

12 Mr. Grace see reminded you have Dr. Domino's
13 testimony that to deal with potency, you can just
14 increase the amount of drug that would be administered.
15 Do you recall that?

16 A. Yes.

17 Q. Do you recall Dr. Domino also testified yesterday
18 if you were concerned about side effects, the solution
19 was to lower the dose?

20 A. That's right.

21 Q. Can you simultaneously raise the dose to get
22 efficacy and lower the dose to avoid side effects?

23 A. It's a bit of a conundrum.

24 Q. Is the issue of trying to take a cholinesterase
25 inhibitor like galanthamine which is weak, what would a

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1 person of skill in the art think about overcoming issues
2 of getting muscarinic, the duration of action, would that
3 appear to be a simple test?

4 A. Well, I mean, given what was published in that
5 literature about low muscarinic efficacy and given what
6 the belief at the time, I'm talking about 1986, based
7 on Bartus and many other articles, you'd want to have
8 something that was really very potent at muscarinic
9 receptors. You'd look at galanthamine and say if I get
10 high enough to really hammer the muscarinic receptors,
11 I'm going to have a lot of nicotinic receptor side
12 effects.

13 MR. SIPES: I have no further questions, your
14 Honor.

15 THE COURT: You may step down.

16 THE WITNESS: Thank you.

17 (Witness excused)

18 - - -

19 MR. SIPES: Your Honor, I will try to clear off
20 the stand.

21 (Pause.)

22 MR. CALIA: Your Honor, plaintiffs would
23 like to call Dr. Karen Kauffman to the stand.

24 - - -

25

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EXHIBIT 5

1 Q. And about how many clients have you had in that
2 period of time?
3 A. Since 1999, approximately 250.
4 Q. Generally speaking, what triggers somebody who
5 contacts you for your long-term care consultant services?
6 A. Most often, it's when the caregiver burden becomes
7 so great that the care being provided in the home is no
8 longer possible, and this usually occurs when behavioral
9 symptoms become so -- so difficult to manage. The other
10 triggering factor is incontinence, which is bowel and
11 bladder, inability to control bowel and bladder.
12 And the other is when someone is requiring
13 assistance to carry out the activities of daily living
14 two to three, at least. Those activities of daily
15 living are bathing, grooming, dress, eating and
16 toileting.
17 Q. You mentioned you have two employers, yourself
18 being one of them. Who's your other employer?
19 A. I'm a full-time faculty at the University of
20 Maryland School of Nursing.
21 Q. And what's your appointment there?
22 A. My appointment, my rank is Associate Professor.
23 Q. Okay. And do you have any other responsibilities
24 aside from being Associate Professor?
25 A. I'm also Program Director of Community Public

EXHIBIT 6

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1 MR. LOMBARDI: It looked okay to me earlier.
2 MR. PAPPAS: Your Honor, just out of curiosity,
3 I'm not sure of the lighting in the courtroom. Is there a
4 way just to dim the lights in one part but not all?
5 THE COURT: Yes. We got that down.
6 (Videotaped deposition played as follows).
7 "Question: Dr. Davis, can you state your name
8 for the record?
9 "Answer: Kenneth Leon Davis.
10 "Question: Can you provide your current home
11 address?
12 "Answer: 160 Cold Spring Road, Syosset, New
13 York.
14 "Question: Can you give us your current
15 business address?
16 "Answer: 1425 Madison avenue, New York, New
17 York.
18 "Question: Dr. Davis, who is your current
19 employer?
20 "Answer: Mount Sinai Medical Center.
21 "Question: Okay. And how long have you been
22 employed by Mount Sinai?
23 "Answer: Since 1979.
24 Question: Dr. Davis, are you employed by either
25 Janssen -- I will break this up.

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1 an understanding as to why your wife would have thought
2 that galanthamine would have been included in the grant
3 application.

4 Answer: No.

5 Question: Do you have any understanding as
6 to why your wife said that she was surprised that
7 galanthamine was not included in the application?

8 Answer: No.

9 Question: So, to the best of your
10 recollection, it was never a possibility that
11 galanthamine was going to be included in the grant
12 application that you sought?

13 Answer: Never the most remote possibility,
14 never even close.

15 Question: The first time that you had a
16 conversation --

17 Answer: Yes.

18 Question -- with your wife about the
19 possibility of her applying for a patent to use
20 galanthamine for the treatment of Alzheimer's disease,
21 do you remember the substance of that discussion?

22 Answer: Yes.

23 Question: And what was that?

24 Answer: I told her, to paraphrase, to stop
25 bothering me about this drug, that it would have no

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1 value unless she got a use patent.

2 Question: Dr. Davis, do you, yourself, have
3 any patents?

4 Answer: No, not that I'm aware of.

5 Question: How did you come to have a
6 knowledge about the existence of use patents?

7 Answer: During the eighties, I started to
8 consult to a lot of drug companies and began to learn
9 about intellectual property through helping them
10 develop various compounds.

11 Question: Why haven't you prescribed a
12 dose of 2,000 milligrams of galanthamine hydrobromide
13 to a patient?

14 Answer: There's no approval at that dose
15 range and there has been no experience at that dose
16 range.

17 Question: Would you have considered or do
18 you consider tacrine to be effective in the treatment of
19 Alzheimer's disease?

20 Answer: I?

21 Question: Yes. After the testing was
22 completed, did you consider tacrine to be effective in
23 the treatment of Alzheimer's disease?

24 Answer: Again, you have to help me more
25 with effective. By effective, do you mean useful?

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1 Answer: My wife told me that.
2 Question: Do you recall when your wife told
3 you?
4 Answer: No.
5 Question: Did you know that physostigmine
6 crossed the blood/brain barrier at the time of your grant
7 application?
8 Answer: Yes.
9 Question: Was crossing the blood/brain
10 barrier a factor in your deciding to work with
11 physostigmine?
12 Answer: Yes.
13 Question: Was this factor important for
14 your decision to work with physostigmine?
15 Answer: Yes.
16 Question: At the time of your writing the
17 physostigmine grant, did you have any markers of
18 physostigmine CNS activity?
19 Answer: Yes.
20
21
22 Question: What were those markers?
23 Answer: Cortisol secretion. That was Bonnie's
24 discovery.
25 Question: So, in fact, Bonnie discovered that

EXHIBIT 7

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1 disease?

2 A. Yes.

3 Q. Do you consider yourself an expert in the treatment,

4 treating drugs?

5 A. Yes.

6 MR. SIPES: I offer this witness as an expert

7 in the clinical testing and development of antimentia

8 drugs including drugs for Alzheimer's disease.

9 THE COURT: Any objection?

10 MS. ULRICH: No objection.

11 THE COURT: Thank you.

12 BY MR. SIPES:

13 Q. We've heard a lot about Alzheimer's disease

14 over the last couple days. Could you very briefly

15 describe the symptoms of Alzheimer's disease?

16 A. Yes. Alzheimer's disease is a disorder

17 characterized by the insidious onset and inexorable,

18 albeit, almost always gradual progression of impairment

19 in first recent memory, then more general memory

20 problems, and accompanied by the onset and progression

21 of deficits in other cognitive symptoms.

22 These include deficits in language of a

23 particular type. They develop a fluent aphasia.

24 Difficulty with executive function, performance of

25 complex tasks. Difficulty coordinating motor activities

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1 with the idea that needs to be performed motorically,

2 known as apraxia, and this constellation of symptoms is

3 often not recognized for a year or even two years by the

4 family, and often even longer by the patient, because

5 another symptom is loss of insight, inability to

6 recognize that one has, indeed, started to suffer loss

7 of very important cognitive functions.

8 And as the disease progresses, there is what

9 one might call secondary, complicating signs and

10 symptoms, that are more in the classically psychiatric

11 realm. These include depression, agitated behavior, and

12 by that I mean irritability, uncooperativeness with

13 necessary care, anger outbursts, disruptions in -- in

14 the ability to sleep and rest, often a pressured

15 need to move and these all -- these secondary symptoms,

16 though we call them secondary, are primary causes down

17 the road, after five, six, seven, eight years or even

18 more, of caregiver exhaustion, which has been discussed

19 earlier, in earlier testimony, and often leads to

20 long-term care institutional placement.

21 Q. The term caregiver burden --

22 A. Yes.

23 Q. -- could you define what that means?

24 A. Yes. As a patient with Alzheimer's disease gets

25 more and more impaired, they need more and more support

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1 and supervision, both to keep them safe, to keep them

2 nourished, to keep them clean from those who have

3 been their lifelong partners, usually their spouse.

4 And I think it was put well by Peter Ravens.

5 This really produces for the caregiver a 36-hour day,

6 you know. It's not just 24 hours a day. It's even more.

7 These patients with Alzheimer's, as the

8 disease progresses, really need constant supervision and

9 what is so heartbreaking is that as the caregiver

10 provides more and more support, the person with

11 Alzheimer's disease is able to provide less and less

12 affection, interest, support for the caregiver, because

13 the parts of one's brain that subsume these functions is

14 also gradually deteriorating.

15 Q. You heard of Peter Ravens' The 36-Hour Day. What

16 is that?

17 A. That's a book that describes and also offers

18 suggestions for caregivers that Peter and a colleague

19 at Johns Hopkins wrote now probably 15 or 20 years ago,

20 which has really become the Bible of the -- of the

21 caregiver support movement. And the -- some of my work

22 with the Alzheimer's association, which was really

23 founded by caregivers in deep distress because of this

24 horrible situation they were in is to try to get them

25 together in group settings or educational settings, to

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1 develop support for them as well as educate them in

2 perhaps better approaches that we in the field as

3 professionals have developed or better approaches that

4 often arise from caregivers own experience that they

5 can share with others.

6 - - -

7 Q. Have efforts been made to measure the caregivers'

8 burden?

9 A. Yes.

10 Q. Can you describe that?

11 A. Well, there are really several actual rating scales,

12 and most of them have tried to quantify the amount of time

13 that caregivers need to spend supervising their -- I'll use

14 the term loved one.

15 It's remarkable how much love exists between

16 caregivers and the loved one who is unable to return their

17 love to the caregiver.

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1 MS. ULRICH: No objection.
 2 THE COURT: Thank you.
 3 DEPUTY CLERK: So marked.
 4 *** (Plaintiffs' Exhibit No. 1321 was received into
 5 evidence.)
 6 BY MR. SIPES:
 7 Q. If you will turn to the second page, Dr. Raskind,
 8 you'll see a heading, Demography.
 9 A. Yes.
 10 Q. And the -- if you could read into the record the
 11 first sentence of the section on demography...
 12 A. Starting with, By most estimates?
 13 Q. Yes.
 14 A. By most estimates, Alzheimer's disease is the cause
 15 of serious confusion and forgetfulness in some 2.5 million
 16 American adults.
 17 Q. Was that believed to be true by those in the
 18 Alzheimer's field in 1986?
 19 A. Yes. And I think that was a conservative estimate
 20 even then.
 21 Q. All right.
 22 A. This is five times the estimate that appeared in
 23 the literature ten years ago, when the National Institute
 24 on Aging began its first studies in this area. Are there
 25 so many more victims now than then? Is there an

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1 Alzheimer's epidemic?
 2 Q. What was the belief of those skilled in the art in
 3 1986 whether there was an Alzheimer's epidemic?
 4 A. There was a belief there was an epidemic, although
 5 part of the vast majority of increased cases was our
 6 ability to recognizing what we had previously been calling
 7 senile dementia, which we attributed to a natural
 8 consequence of the brain aging process, was, indeed, a
 9 specific disease, Alzheimer's disease.
 10 Q. And was there an understanding of how the incidence
 11 of Alzheimer's disease increases with age?
 12 A. Yes, there is.
 13 Q. How does it increase with age?
 14 A. Well, it -- it increases or it doubles
 15 approximately every five years after the age of 60.
 16 Q. And what are the odds of -- do you know what the
 17 odds of having it roughly at the age of 80 or '85?
 18 A. Well, the estimates all are very high. They vary
 19 somewhat, but if one is fortunate enough to live to 85,
 20 at that point and I don't know, your risk is at least
 21 30 percent. And some estimate it's as high as 40 percent
 22 or even 50 percent.
 23 Q. And then if you will look at the next section, which
 24 is the cost of Alzheimer's disease, did the NIA estimate
 25 what the cost of, or did they report an estimate of the

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1 cost of Alzheimer's disease to our society?
 2 A. Yes, they did.
 3 Q. And what was their report?
 4 A. They estimated that \$35 billion was spent last
 5 year. I'm presuming that's 1985, on the care of
 6 Alzheimer's patients. This includes the cost of nursing
 7 home and other long-term medical care, but does not begin
 8 to account for the emotional and social costs of the
 9 disease and also probably didn't account for what were
 10 called the indirect costs, if you will, of -- and that's
 11 addressed in the next paragraph when NIA health economist
 12 Dr. William Cartwright suggests that 35 billion, just
 13 quoting him, is the tip of the iceberg.
 14 Dr. Cartwright and his colleagues, Dr. Wang
 15 of Howard University in Washington, D.C. and Dr. Hu of
 16 Pennsylvania State University in State College,
 17 Pennsylvania, estimate the special services required by
 18 dementia patients might cost more than \$38 billion, with
 19 another \$39 billion for what the investigators call
 20 indirect costs.
 21 That's the value of the time of informal
 22 caregivers. That's the family. Not so informal. The
 23 family is dedicating to this effort.
 24 Q. At the time, was there, then, a sense of the --
 25 that the Alzheimer's disease epidemic was imposing

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1 tremendous costs on society?
 2 A. Right. A tremendous cost then and an ever-
 3 increasing one.
 4 Q. And what was the response of the medical community
 5 to this growing epidemic?
 6 A. Well, the -- the response of the medical community
 7 was -- it was, I think, interesting, putting myself back
 8 at that time and I did spend a lot of time with the
 9 general medical community. They recognized the problem,
 10 but were I'm not sure if cynical is the right word, but
 11 were skeptical that there was really anything we could do.
 12 They were supportive of general research,
 13 trying to find something, but they were really skeptical
 14 that we had anything to offer that was worth, worth the
 15 cost and the effort.
 16 Q. Were there any approved treatments for Alzheimer's
 17 disease at the time?
 18 A. There were none.
 19 Q. Were there any drugs that were perceived as
 20 treatments for Alzheimer's disease?
 21 A. There were none.
 22 THE COURT: Mr. Sipes, I've got a 4:30
 23 criminal proceeding. We're taking a half an hour break,
 24 coming back at 5:00 o'clock.
 25 MR. SIPES: Thank you.

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1 Q. Who was Dr. Leber?

2 A. Dr. Leber was the Director of the Peripheral and

3 Central Nervous System Division or Neuropharmacology

4 Division of the FDA.

5 Q. Is that the division that has responsibility for

6 antimentia drugs?

7 A. Yes.

8 Q. Would that be the division that had responsibility

9 for drugs to treat Alzheimer's disease?

10 A. Yes.

11 Q. So would Dr. Leber be somebody who was

12 knowledgeable in the field about the treatment of

13 Alzheimer's disease?

14 A. Yes.

15 Q. If you will turn to Page 10, you'll see, beginning

16 at Line 2, the statement, at this point in time, even a

17 safe and effective symptomatic treatment for some cardinal

18 sign and symptom of Alzheimer's would constitute a

19 substantive therapeutic advance.

20 Do you see that?

21 A. Yes, I do.

22 Q. Was that a widely held view that in 1989, even a

23 safe and effective symptomatic treatment for some cardinal

24 sign and symptom of Alzheimer's would constitute a

25 substantive therapeutic advance?

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1 A. Absolutely. I think that view is universal.

2 Q. The reference for some cardinal sign and symptom

3 of Alzheimer's, what would that refer to?

4 A. I think above all, memory impairment.

5 Q. And if you will turn to Page 17, at the bottom,

6 beginning on Line 21, you'll see a statement, My

7 colleagues and I have sought to reassure those interested

8 in developing antimentia drugs that the lack of an

9 approved antimentia drug is a reflection of the

10 inadequacies of the drugs so far tested, not of our

11 assessment methodologies or implied regulatory biases.

12 What was Dr. Leber saying there?

13 A. What Dr. Leber was saying -- and I totally believe

14 that he felt this wholeheartedly -- that he and the FDA

15 were as much concerned about bringing an effective,

16 tolerable and safe treatment for Alzheimer's disease to

17 the public as anybody else, but that the feeling that the

18 FDA was somehow setting barriers to doing that was

19 misguided.

20 Q. And do you see his reference to the inadequacies of

21 the drug so far tested?

22 A. Yes.

23 Q. Would Dr. Leber have been knowledgeable about the

24 work done on physostigmine?

25 A. Yes, he would have. He was a, and still is, a man

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1 Q. Was it a widely-shared view at the symposium that,
2 in your opinion, there were no lead drugs for Alzheimer's
3 disease?
4 A. Yes.
5 Q. And in your opinion, did that pose challenges for
6 developing drugs for Alzheimer's disease?
7 A. Well, I think it posed a challenge simply because
8 if you -- if you don't have something that appears
9 promising, it's hard to know where to go at least in
10 clinical trials in people. You have to start at ground
11 zero.
12 Q. I will ask you to turn to Page 37. You'll see
13 there's, beginning at Line 20, some testimony by Dr.
14 Drachman.
15 A. Yes.
16 Q. Who is Dr. Drachman?
17 A. Dr. David Drachman was a prominent neurologist
18 interested in geriatric neurology at the University of
19 Massachusetts.
20 Q. And is that the same Dr. Drachman that has been
21 cited as doing some of the early work on developing the
22 cholinergic deficit hypothesis for Alzheimer's disease?
23 A. Yes, at least for -- of cognitive loss in normal
24 aging and by extrapolation of Alzheimer's disease.
25 Q. If you will turn to Page 38, beginning at Line 2,

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1 you'll see the statement by Dr. Drachman: We don't have
2 any drugs that are really doing a hell of a lot.
3 Do you see that?
4 A. Yes. I not only see it, but I can actually hear
5 him saying it.
6 Q. Do you recall him saying that?
7 A. I do.
8 Q. Did you understand Dr. Drachman to be expressing
9 skepticism about the currently available drugs that were
10 in development for Alzheimer's disease?
11 A. Yes.
12 Q. On Page 39, you'll see, beginning at Line 17, there's
13 testimony by Dr. Wurtman.
14 A. Yes.
15 Q. Who was Dr. Wurtman?
16 A. Dr. Wurtman was a neuroscientist at the Massachusetts
17 Institute of Technology.
18 Q. Is that the same Dr. Wurtman that we heard about
19 earlier today, who published a paper reviewing the
20 various theoretical ways in which the cholinergic deficit
21 in Alzheimer's disease might be addressed?
22 A. Yes.
23 Q. If you will look at Page 40, beginning at Line 3,
24 you'll see testimony from Dr. Wurtman. We have no lead
25 drug that has been shown to affect the patients and to

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1 core symptom?
2 A. Yes.
3 Q. In 1986, with regard to a person of ordinary skill
4 in the art, is that how they would have understood the
5 core symptom of Alzheimer's disease?
6 A. Yes.
7 Q. And, by the way, when Dr. Thal refers to dementia
8 there in the course of memory, did you understand him to
9 be referring to a specific kind of dementia?
10 A. No.
11 Q. Let me ask you to turn to Page 95, beginning at
12 Line 18. You'll see a statement, secondly, you need to
13 say something about what is happening to that patient
14 in an overall global sense or in activities of daily
15 living, and that the drug must show improvement in both
16 areas. If you can't show cognitive improvement, and
17 you can't show improvement in overall functioning, you
18 don't have a drug to treat dementia.
19 Do you see that?
20 A. Yes.
21 Q. Was that a widely-shared view about what it meant
22 to treat dementia?
23 A. Yes, it was.
24 Q. Would that have been the understanding of what it
25 meant to treat dementia in 1986 by those of ordinary

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1 skill in the art?
2 A. Yes.
3 Q. Could you explain what Dr. Thal is saying about the
4 need to show both cognitive improvement and an improvement
5 in overall functioning?
6 A. Well, he's saying that if one shows a modest
7 improvement on some cognitive reading or performance
8 scale, but there is no evidence that the drug is also
9 improving overall daily function, either in activities
10 of daily living or the observational judgment of the
11 caregiver or another person living with the patient,
12 that, yes, indeed, they are doing better in their day-
13 to-day activities and life, then you don't have a drug
14 which can be considered effective.
15 Q. If a drug were to show a patient having improvement
16 in a memory test but not in overall functioning, would
17 that be considered a treatment of dementia by a person
18 of ordinary skill in the art in 1989?
19 A. It would not.
20 Q. Let me ask you to turn to the next page, Page 96.
21 There's a statement by Dr. Thal beginning at Line 3:
22 All of the drugs that we are currently testing are
23 really drugs designed to induce acute improvement in
24 patients. But they are not designed to change the
25 natural history of the disease.

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1 A. No.

2 Q. Let me ask you to turn to the category of drug
3 therapy, metabolic enhancers.

4 Would you explain what that category is
5 referring to?

6 A. Yes. Well, the neurons in Alzheimer's disease were
7 obviously decreasing in number because they were becoming,
8 if you will, sick, and dying. And the hope was that the
9 neurons that were still alive might function better if
10 they were able to produce more energy. So if an
11 individual neuron produced energy more efficiently, then
12 it could do its job of communicating with other neurons
13 to produce what we see clinically as memory function and
14 other cognitive functions.

15 Q. So were the metabolic enhancers, were they attempted
16 as a cure for Alzheimer's disease?

17 A. No.

18 - - -

19 Q. They were a symptomatic treatment like the cholinergic
20 strategy?

21 A. Yes.

22 Q. If you would look to the discussion of the ergoloid
23 mesylates...

24 What drug is that referring to?

25 A. That is referring to a drug that was marketed under

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- 1 A. Yes.
- 2 Q. What was viewed as promising?
- 3 A. There were some anecdotal case series reports that
- 4 it was helpful and even some placebo controlled data with
- 5 subjective rating scales, if I'm recollecting correctly,
- 6 that suggested that there was some improvement with this --
- 7 this drug's administration to patients with Alzheimer's
- 8 disease.
- 9 Q. And is it correct that there were several
- 10 pharmaceutical companies developing newer homologs of
- 11 piracetam?
- 12 A. Yes.
- 13 Q. Do you recall what some of those homologs were?
- 14 A. The one we were involved in studying was oxyracetam
- 15 and I believe Ciba-Geigy launched a major multi-center
- 16 trial to determine if oxyracetam were indeed an effective
- 17 managed treatment for Alzheimer's disease.
- 18 Q. So you were involved in the trial?
- 19 A. Yes. We participated in that trial.
- 20 Q. And when was this that oxyracetam was tried as a
- 21 treatment for Alzheimer's?
- 22 A. This was I think in the late 1980s.
- 23 Q. And when you participated in the trial, did you view
- 24 it as a promising treatment for Alzheimer's?
- 25 A. Yes, I did.

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- 1 Q. And was it a symptomatic treatment or a cure?
- 2 A. Symptomatic.
- 3 Q. Did oxyracetam succeed as a treatment?
- 4 A. No.
- 5 Q. Did you view it as a failure?
- 6 A. Yes.
- 7 Q. Was the failure of oxyracetam, would that have been
- 8 predictable to a person of ordinary skill in the art in
- 9 1986?
- 10 A. No.
- 11 Q. I take it when you decided to participate in the
- 12 trial, did you predict it would fail?
- 13 A. No, we did not.
- 14 Q. As a general matter, when you participate in a
- 15 clinical trial, do you make any judgment about the
- 16 possibility of success before deciding whether or not to
- 17 participate?
- 18 A. Well, we have hope, based on often the animal
- 19 studies, the pre-clinical studies that are done that show
- 20 improvement in cognitive function and in species other
- 21 than humans, and also data supporting the potential safety
- 22 of the drug. Hope springs eternal, so we keep trying.
- 23 In the clinic, we were discouraged, but we
- 24 were discouraged because we didn't have anything that
- 25 worked. And that meant energy should be put into

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1 which are just being recognized at that time as, in fact,
2 meeting all the criteria for neurotransmitters.

3 And, finally, neuronal protectors. Could you
4 find ways to enhance the resiliency of neurons so that
5 whatever the basic pathogenic process was that was
6 attacking neurons in Alzheimer's disease, the neurons
7 would be more resistant or able to compensate or maybe
8 enable to build new processes that had been destroyed.

9 Q. And the different types of -- the various types
10 of attempts, were those attempts at cures for Alzheimer's
11 disease or attempts at symptomatic treatment?

12 A. They were attempts at symptomatic treatment.

13 Q. And I notice there's a whole list of them.

14 Did any of the ones that were tried before
15 1986 succeed?

16 A. No.

17 Q. Did they all fail before 1986?

18 A. Well, many of them continued to be studied for
19 substantial periods of time after 1986.

20 Q. And by 1986, would a person of ordinary skill in
21 the art in January 1986 be able to predict which of
22 these -- well, predict that all of them would fail?

23 A. No. They would not. And, you know, all of them
24 individually had their proponents.

25 We heard that at the -- in Detroit, at the

1

2 Q. Were various ways of increasing blood flow to the
3 brain tried after 1986?

4 A. Yes.

5 Q. A person of ordinary skill in the art in 1986
6 confronted with all of these different ways of trying to
7 provide symptomatic relief to a patient with Alzheimer's
8 disease, could he or she predict which of these approaches
9 would succeed?

10 A. No, he or she could not.

11 Q. Let me ask you to turn back to the Swaab and Fliers
12 article and look at Page 419, where the heading is
13 Neurotransmitter Substitution.

14 MR. SIPES: I've been asked to identify that
15 as Exhibit 1401 and to offer to the Court in its
16 discretion as a summary of the treatment attempts that
17 we will promise to offer in smaller form.

18 THE COURT: Are we back to figuring out
19 which demonstratives come out?

20 MS. ULRICH: I'm a little confused, because
21 the copy of the demonstrative I received, it looked like
22 what was up on the screen but now it looks like this.
23 I'm kind of confused what was up on the screen.

24 MR. SIPES: Why don't we try to work it out
25 and get it resolved by tomorrow. I'm afraid there was

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1 Lafayette Clinic, they were looking at a combination
2 of Lecithin and one of the nootropic drugs.

3 And so there was, A, no consensus, but, B,
4 lots of opinion.

5

6 Q. Were there people who tried neuronal protectors
7 after 1986?

8 A. Yes.

9 Q. Were there people who tried neuropeptides after
10 1986?

11 A. Very much so.

12 Q. Were there people who tried amines after 1986?

13 A. Yes.

14 Q. Were there people who tried the cholinergic approach
15 after 1986?

16 A. Yes.

17 Q. Were there people that tried metabolic enhancers
18 such as nootropics after 1986?

19 A. Yes.

20 Q. Were there people that tried neurotransmitter
21 enhancers after 1986?

22 A. Yes.

23 Q. Were there various ways, including blood?

24 A. Yes.

25

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1 Q. Let me ask you to turn to Swaab and Fliers'
2 conclusion about cholinergic substitution therapy.
3 Would you look at Page 419, the paragraph on the
4 right-hand column?
5 A. Yes.
6 Q. Again, to be clear, this includes precursors,
7 cholinesterase inhibitors, and agonists on the category
8 of cholinergic substitution therapy?
9 A. That's right. They also talk about cholinesterase
10 inhibitors as well.
11 Q. Could you read that into the record, the paragraph,
12 in conclusion?
13 A. Yes. In conclusion, although some clinical
14 improvement can occasionally be seen, and they quote
15 Barbeau in 1978, a satisfactory treatment of the
16 cognitive impairment of Alzheimer's disease by means
17 of pharmacological substitution for deficits in the
18 cholinergic system seems at present not to be feasible.
19 Q. Do you understand Swaab and Fliers to be expressing
20 skepticism for prospects?
21 A. Yes.
22 Q. Using cholinergic agents to cure Alzheimer's disease
23 or to treat --
24 A. No. To treat Alzheimer's disease.
25 Q. They're skeptical that cholinergic will even be a

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1 treatment?
2 A. That's correct.
3 Q. Let me ask you to turn to Page 421. At the top of
4 the left-hand column of 421, you see there's a statement,
5 There are also some general considerations that make
6 neurotransmitters substitution an enterprise with only
7 a limited chance of success.
8 Do you see that?
9 A. Yes, I do.
10 Q. And again the reference to neurotransmitter
11 substitution, that would include cholinergic agents?
12 A. Yes.
13 Q. Do you have an understanding of what are the
14 considerations Swaab and Fliers were saying what gives
15 a strategy only a limited chance of success?
16 A. Yes.
17 Q. Could you describe what they are?
18 A. They, I think, describe accurately that there's
19 not just a single, simple cholinergic system but,
20 rather, there are multiple components of this
21 acetylcholine using group of neurotransmitter systems
22 and that, you know, as we learn more about the
23 neurochemistry of the brain, you know, we recognize that,
24 you know, there are cholinergic nuclei in the -- in the
25 septal nuclei as well as in the nucleus basalis and

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1 A. Yes.

2 Q. What would that tell a person of ordinary skill in
3 the art about the location in the body of galanthamine's
4 principal effects?

5 A. These are all disorders of the body outside of
6 the central nervous system, outside of the brain.

7 Q. And what would be described as -- what would a
8 description of galanthamine above all for diseases of
9 the body as opposed to the brain, what would that say
10 to a person of ordinary skill in the art about the
11 prospects for using galanthamine as a treatment for
12 Alzheimer's disease?

13 A. It would diminish interest because in terms of
14 strategies to enhance any neurotransmitter system and
15 certainly the cholinergic system and certainly for
16 cholinesterase inhibitors, we were trying to find
17 compounds that had substantially more activity in the
18 brain, where we wanted to get therapeutic effect on
19 memory and other cognitive functions, with low or
20 hopefully minimal effect on the periphery, because the
21 periphery is where we experience these side effects
22 that made these drugs so difficult to use.

23 Q. Now, if you will turn to the fourth page, it
24 doesn't have page numbers, but it's Mylan Bates number
25 05986.

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1 A. Got it.

2 Q. There's a -- the middle paragraph that begins, The
3 findings.

4 A. Right.

5 Q. Let's blow that up. It begins, The findings from
6 treating diseases involving the central motor neuron, a
7 total of 64 cases in all, are less straightforward.

8 A. Yes.

9 Q. Then there's a discussion of infantile cerebral
10 palsy.

11 A. Yes.

12 Q. Do you recall defendants' experts pointing to this
13 discussion of infantile cerebral palsy as support for
14 galanthamine's use in Alzheimer's disease?

15 A. Yes. Yes, I remember. I didn't follow the logic,
16 but I remember the statement.

17 Q. In your opinion, does that discussion of
18 galanthamine's use in infantile cerebral palsy, would
19 that suggest a person of ordinary skill in the art to
20 use galanthamine for Alzheimer's disease?

21 A. No.

22 Q. Why not?

23 A. Multiple reasons. First of all, this is cerebral
24 palsy, which is a disorder of the upper motor neurons,
25 critical neurons that control movement. This is not a

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1 cognitive disorder.

2 Now, admittedly, some children, and we're
3 talking about children here, so childhood Alzheimer's
4 disease is extreme extremely rare. As a matter of fact,
5 has not yet been reported. But be that as it may, when
6 you have children who have usually neonatal hypoxia
7 causing cerebral palsy, sure, some of these kids may
8 have subtle changes or deficits in cognitive function,
9 but basically they're talking about motor function here.
10 And even though they talk about the central motor neuron,
11 what they are seeing and they're observing, I don't know --
12 it's not compared to placebo. I don't know if there's
13 any validity to these observations, actually a result of
14 the drug.

15 The first one they list is improvement
16 manifested in diminished spasticity.

17 Now, spasticity is something that the
18 physical medicine and rehabilitation doctors who take
19 care of people with cerebral palsy treat, you know,
20 they treat with some medications. Most of these are
21 muscle relaxants. They also use actual physical
22 therapy, physical exercise and stretching of the joints
23 and the muscles to get improvement.

24 So this -- you know, this is really talking
25 about applying this medication, galanthamine, to a

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1 disorder, to the -- to the outside of the brain physical
2 manifestations of cerebral palsy.

3 Q. And are you -- is there any connection in terms
4 of pathology between infantile cerebral palsy and
5 Alzheimer's disease?

6 A. No.

7 Q. Would a person of ordinary skill in the art in
8 1986 that saw something being used as a treatment for
9 infant cerebral palsy, would they think it would have
10 relevance to Alzheimer's disease?

11 A. No.

12 Q. Have you ever seen, in your research on Alzheimer's
13 disease, have you ever seen the Pernov article cited as a
14 relevant source for Alzheimer's disease?

15 A. I have not.

16 Q. And let me ask you to turn to the section on
17 application and dosage.

18 A. Yes.

19 Q. If you can pull up the bottom paragraph there.

20 Do you recall actually defendants' counsel
21 earlier today referring to this reference to the daily
22 dose of giving two to three times at intervals of twelve
23 or six hours?

24 A. Yes.

25 Q. I think defendants' counsel was suggesting that

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1 would have a bearing on the duration of action of
2 galanthamine?

3 Do you recall that? Do you recall that?

4 A. Yes, I do.

5 Q. Do you believe that -- well, first of all, what
6 sort of action is being described in this paragraph?

7 A. I don't have a clue. You know, I've looked, tried
8 to look carefully at that and it's not at all clear what
9 the readout is, what the end point is that would suggest
10 how long a drug is working. They simply say this is what
11 they do. And, you know, I think that's -- this is an
12 interest in terms of toxicity, because they don't seem
13 to be stating that there's toxicity when they give, you
14 know, children 15 to 30, up to 30 milligrams per day.
15 But it certainly doesn't say anything about duration of
16 action because we don't know what the action is.

17 Q. Would a person of ordinary skill in the art reading
18 this in 1986, would he or she be able to conclude anything
19 about the duration of action of galanthamine from that
20 paragraph?

21 A. No, they would not.

22 Q. In your opinion, are there other sources in the
23 prior art that would tell a person of ordinary skill in
24 the art that the duration of action for galanthamine
25 was shorter than twelve or six hours?

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1 A. Yes.

2 Q. What sort of reference?

3 A. I think, you know, actually, for central nervous
4 system effects, the best source is Cozanitis.

5 Q. And what duration does that show?

6 A. Well, he looked at the readout was
7 electroencephalographic changes to photic stimulation
8 and also changes in disruption of, or reinstitution of
9 alpha rhythm. And he had a duration of action that was
10 less than 30 minutes.

11 Q. And --

12 A. In the specific system.

13 Q. And do you recall Dr. Domino's 1988 review of the
14 literature of galanthamine for purposes of considering
15 its use for Alzheimer's disease?

16 A. Yes, I do.

17 Q. And --

18 A. I thought it was an excellent review.

19 Q. And do you recall his conclusion for that use in
20 1988 being that galanthamine had a duration of action
21 similar to physostigmine?

22 A. Yes.

23 Q. Do you believe that a person of ordinary skill in
24 the art in 1986 would have come to the conclusion, as Dr.
25 Domino did, that galanthamine had a duration of action

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1 galanthamine?
2 A. Well, my observation is that this drug is -- is helpful
3 in stabilizing the progression of Alzheimer's disease. It's
4 the impression both of myself and our group that persons on
5 galanthamine as well as perhaps other cholinesterase
6 inhibitors, have a slower rate of deterioration compared to
7 our practice before galanthamine and other cholinesterase
8 inhibitors were introduced.
9 Q. Now, I note that the study that you were referring to
10 is USA one study group.
11 A. Yes.
12 Q. What does that refer to?
13 A. That was one of the large multi-center trials that were
14 carried out in drug --
15 Q. How many were carried out?
16 A. My understanding is that there were four.
17 Q. And what were the results of the other trials?
18 A. The other trials were all consistent with this trial.
19 All the trials showed benefit compared to placebo in
20 cognitive function as well as overall global assessment of
21 function.
22 Q. And which domains of cognition did the other trials
23 show improvement in?
24 A. They showed, I think the ADASC. That focuses
25 substantially on memory.

1 the same as it had been at baseline, one year earlier, so
2 there was a stabilization for 12 months of cognitive function
3 with galanthamine.

4 The second finding, and this was actually
5 unexpected because we all believed that this was a
6 symptomatic treatment that merely would rev up the ability to
7 use cognitive function but not affect the course of illness.

8 The second finding was that persons who were
9 started on placebo, who were then switched to galanthamine
10 six months later, who we predicted when they switched to
11 galanthamine would catch up to the level of cognitive
12 function of those who had been started on galanthamine six
13 months earlier, in fact, failed to catch up.

14 They seemed to, during that six months placebo,
15 have lost something, so that their potential to improve with
16 galanthamine was reduced. Now, they did improve when they
17 were placed on galanthamine, but their improvement was not to
18 the level of persons who had already been on galanthamine six
19 months earlier.

20 Q. Did you do any further extension studies to examine
21 this effect?

22 A. Yes. Well, I thought it was very interesting and
23 the -- the company decided to, as rigorously as they could,
24 follow people on open label galanthamine long term. And I
25 think their original motivation, if I recall correctly, was

1 THE WITNESS: I had a sense I was going to fall
2 down the stairs. Comic relief here.
3 (At this point the witness then stepped down from
4 the witness stand.)
5 BY MR. SIPES:
6 Q. Could you please explain what Figure 1 shows?
7 Doctor Raekin, please be sure to keep your
8 voice up because you're away from the mikes.
9 A. I will do my best using my pointer.
10 This is the figure from the manuscript, and I
11 think the first thing to understand is that the six-month
12 placebo data are here (indicating), from the original study,
13 and this is the six-month data from the long term -- from the
14 open label six-month extension.
15 So we have 12 months of data and that simply
16 again shows that at 12 months -- and this is a very
17 important thing for persons with Alzheimer's disease and
18 their families. They have no deterioration at 12 months
19 compared to baseline.
20 And then the study is carried out for 36 months.
21 And we got additional Alzheimer's disease assessment
22 cognitive subscale ratings at two years, 24 months, and then
23 at three years, 36 months.
24 So we have the ability to look at the slope or
25 the -- or the degree of change in these persons.

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1 And then, for comparison, we did, and this was
2 something I pushed hard for people to do. We did the best
3 we could in determining placebo, and we have really three
4 types of placebo data. But before I go into it, they all
5 fall on exactly the same line or at least the same line
6 projected out.
7 So I think and many other people think that all
8 of these placebo data are representative of the natural
9 history of untreated Alzheimer's disease.
10 The first data are the six month data from the
11 year 2000 study in neurology.
12 Then we had data from a failed study that was
13 done by Janssen, oh, two or three years before, with a drug
14 called sibelusol (phonetic), which was supposed to decrease
15 neurofibrillary tangle formation, but that's another story.
16 In that study, that study was started before
17 any cholinesterase inhibitor had been approved, so
18 institutional review boards said it's okay to keep people
19 on placebo for a full year. Donepezil was approved, then
20 Institutional Review Board said there really is available
21 treatment. It's not ethical to keep people on treatment
22 for that long.
23 But we had this sabeluzole from people with
24 Alzheimer's disease who were socioeconomically almost
25 superimposed on the group with galanthamine. When you look

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1 across Alzheimer's studies in this country, the data look
2 very similar, from one study to another. So actually they
3 are fairly comparable.
4 So we had one year. As you can see, compared
5 to six months, the difference between galanthamine and
6 placebo starts to become greater, even at this point.
7 Then we used a mathematical projection, which is
8 really what I call a kind of wait list control group. So in
9 studies of psycho therapy today, the control -- you can't put
10 a person who's being studied with psycho therapy on a placebo
11 pill because they're not getting an active pill, so they
12 often use things like a waitless control. They have people
13 wait to enter psycho therapy for a period of time. They get
14 the natural course of illness. Then they compare it to what
15 happens with psycho therapy.
16 Here, we have data which was collected actually
17 at Mount Sinai by Dr. Davis, Dr. Mohs' group, on persons on
18 the ADAS cog, because that's where the ADAS cog was developed
19 at Mount Sinai by psychiatrist LaRosa.
20 They collected data every six months on these
21 people who were untreated because there was no treatment at
22 that time. And using this large database, a resident, Dr.
23 Stern, developed a mathematical projection.
24 So if you had an ADAS cog at 20, at some point
25 you would be able to predict every year how much you would

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1 deteriorate. And the prediction he came up with when you
2 had a mental state around 30 -- I'm sorry -- the ADAS cog
3 around 30, which was about the baseline in these, you'd
4 decline about seven points every year over the next three
5 years. And that's plotted out here (indicating).
6 And this has been validated multiple times by
7 the Alzheimer's disease cooperative study. Our studies --
8 everything from estrogen to prednisone. Seven points a year
9 on the ADAS cog for people at this stage of Alzheimer's
10 disease is a pretty darn good estimate.
11 So this is placebo group projected out two years,
12 so a waitless placebo. And you would predict someone would
13 decline 20 points on the ADAS cog or actually increase in 20
14 points, because on the ADAS cog, higher is worse, whereas if
15 one stayed on galanthamine, the decline was really cut in
16 half.
17 And these data are, to me, very telling. I mean,
18 what you want to do in most chronic degenerative diseases, no
19 matter what part of the body they affect, is to slow the rate
20 of decline. That's really what we do with statins.
21 Lipitor. You look at the advertisement on television. You
22 figure you take Lipitor and your coronary arteries are going
23 to open up and you're going to be able to run a marathon even
24 though you have trouble walking around the block. But in
25 reality, what Lipitor does is the very same concept. Lipitor

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1 slows the rate of decline in the size of our coronary
2 arteries over years. So if you take Lipitor, and I'm very
3 close to this issue myself, not to overshare, but you
4 actually don't cure or reverse coronary artery disease, you
5 simply slow the rate of progression of narrowing of the
6 coronary artery.

7 And that's exactly, I submit to the scientific
8 community, what we're seeing with this cholinesterase
9 inhibitor and perhaps other cholinesterase inhibitors as well
10 although the data aren't quite as impressive for the other
11 two that are currently used.

12 Q. Let me ask you to turn to the next page to look at
13 Figure 3.

14 A. I should go back?

15 Q. No.

16 A. Stay here?

17 Q. Figure 3. If you can explain what that shows?

18 A. Yes. So, you know, when I first saw the data that were
19 on the previous slide, I said, I know what's going on here.
20 This is really an artifact, because, you know, over time we
21 had some dropouts. You always have some dropouts in a study
22 and I felt that it was possible that the persons who had the
23 inherently more aggressively deteriorating course would drop
24 out, they would get discouraged or the families would get
25 discouraged, which would leave a group of persons who were

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1 inherently slower decliners, if you will, and that's what
2 would kind of artificially move the curve upward.
3 So I said I'm not getting involved in this
4 situation unless you look at the data from the dropouts while
5 they were still on galanthamine, before they dropped out, to
6 see if their rate of decline was steeper than the persons who
7 hung in there for the full three years.

8 And we had the data, at least up to two years,
9 obviously on the dropouts, and the dropouts are the dotted
10 line. You can't get data at the end because they dropped
11 out somewhere along the line.

12 But it turned out, in fact, that the rate of
13 decline of the dropouts, while they were still in the
14 galanthamine study, was exactly the same as the rate of
15 decline of those who hung in for the full three years of
16 the study.

17 - - -

18 A. (Continuing) So I think these findings are real and as
19 rigorous as one can do, given the ethical constraints of
20 doing long-term controlled placebo study in Alzheimer's
21 disease.

22 - - -

23
24
25

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1
2 (At this point the witness then resumed the
3 witness stand.)
4 BY MR. SIPES:
5 Q. And let me look on the first page in the summary under
6 conclusions.

7 Doctor, if you could just read your
8 conclusions...

9 A. Cognitive decline over 30 signals months of continuous
10 galanthamine treatment was substantially less than the
11 predicted cognitive decline of untreated patients with mild
12 to moderate dementia. Thus, the cognitive benefits of
13 galanthamine seemed to be sustained for at least 36 months.
14 These findings suggest that galanthamine slows the clinical
15 progression of Alzheimer's disease.

16 Q. Do you still agree with those conclusions?

17 A. Yes, I do.

18 Q. Do you think those conclusions are accepted as good
19 science in the field?

20 A. Yes, I do.

21 Q. Have you seen the behavior of doctors change with
22 regard to when they prescribe cholinesterase inhibitors as a
23 result of these sorts of studies?

24 A. Yes. Slowly, but inexorably, the prescribing of
25 cholinesterase inhibitors has done two things: One, doctors

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1 are starting earlier, and they're also hanging in there.

2 There was some very misleading, in my opinion,
3 misleading advice from some parts of the scientific
4 community that if you don't see improvement on a
5 cholinesterase inhibitor after six months, you should stop
6 the drug.

7 Well, you don't see improvement because we don't
8 have a marker going back to the Lipitor analogy, we don't
9 have a marker like blood cholesterol. What keeps people
10 enthusiastic about their statin drug is that their
11 cholesterol drops and you can measure this very easily,
12 but Alzheimer's is a disease of the brain and the brain is
13 inside the skull. It's very difficult to take a sample.
14 It's not reflected in think biologic marker.

15 So people were saying, well, a person is not
16 getting better. But even though the drug was working to
17 slow the rate of decline, which was -- it really seems to me
18 what the actual target of treatment is, but now I think that
19 the ship is turning around in terms of the conception of what
20 we're doing with these drugs.

21 Q. And let me ask one question just to clarify the
22 record. You refer to a Dr. Davis as having developed
23 this placebo. There have been several Dr. Davises in this
24 case.

25 A. Yes.

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1 Q. And what you since learned about tolerance to
 2 galanthamine?
 3 A. Well, it's well tolerated in terms of adverse effects
 4 or anything.
 5 Q. Now, you recall that defendants' experts have testified
 6 about the ability of a doctor to find a dose.
 7 A. Yes.
 8 Q. The dosing from the patent?
 9 A. Yes.
 10 Q. Have you looked at the dosing in the patent?
 11 A. Yes, I have.
 12 Q. In your opinion, would a person of ordinary skill in
 13 the art be able to administer galanthamine in a
 14 therapeutically effective dose in 1986, a person of ordinary
 15 skill in the art?
 16 Let me start that question over. I think I
 17 reiterated it about three times.
 18 Would a person of ordinary skill in the art in
 19 1986 reading the patent be enabled to administer galanthamine
 20 in a therapeutic dose?
 21 A. Yes, they would.
 22 Q. How would he or she do so?
 23 A. Well, they would start at a low dose, as described in
 24 the patent, and then they would gradually titrate the dose
 25 upward to a point where they either saw therapeutic effects

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1 or the patient developed adverse effects, which were
 2 troublesome enough to stop any further increase of the
 3 medication.
 4 Q. And was that technique of titration, was that
 5 well-known to a person of ordinary skill in the art in
 6 1986?
 7 A. Yes. In geriatric medicine, the mantra is start low
 8 and go slow, but go.
 9 So we often make a mistake in geriatric medicine,
 10 because we're so worried about side effects, starting with a
 11 low dose and then forgetting to titrate. That's one of the
 12 things that we constantly have to keep in mind. You know,
 13 it's always a balance between therapeutic effects and adverse
 14 effects, but you have to remember that you are trying to get
 15 therapeutic effects.
 16 Q. And does the patent anywhere describe the technique of
 17 titration?
 18 A. Yes, it does.
 19 Q. Where does it do so?
 20 A. So on -- on the left-hand column on the first page,
 21 Line 64 and 65, it may be necessary to begin at lower doses
 22 than are ultimately effective. And to me, that really
 23 applies to titration.
 24 Q. And would a person of ordinary skill in the art reading
 25 the patent understand that to refer to titration?

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1 A. Yes, they would.
 2 Q. Now let me ask you, generally, would a person of
 3 ordinary skill in the art in 1986 reading the patent be
 4 enabled to practice the claimed invention by administering
 5 galanthamine as a treatment for Alzheimer's disease?
 6 A. Yes.
 7 Q. Let me now turn you to what a person of ordinary skill
 8 in the art would understand from what the patent is saying.
 9 And let's start with the background.
 10 MR. SIPES: If you could put the first paragraph
 11 under background up...
 12 BY MR. SIPES:
 13 Q. Do you see that first paragraph? There's a discussion
 14 of two Cozanitis articles?
 15 A. Yes.
 16 Q. And then there's a conclusion that these studies show
 17 an increase in both plasma cortisol and plasma ACTH when
 18 galanthamine was administered to patients together with
 19 atropine?
 20 A. Yes.
 21 Q. Would a person of ordinary skill in the art in 1986
 22 know about the drug atropine?
 23 A. Yes.
 24 Q. What would he or she know about atropine?
 25 A. It's a classic muscarinic cholinergic antagonist.

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1 Blocks the effects at one of the two major receptors.
 2 Q. Would a person of ordinary skill in the art in 1986
 3 know that?
 4 A. Yes.
 5 Q. What would a person of ordinary skill in the art in
 6 1986 understand about galanthamine from the first paragraph?
 7 A. Well, they would understand -- several things. The
 8 first was that because ACTH is centrally regulated, and its
 9 release is -- is regulated by the brain and by -- through a
 10 cholinergic mechanism, that galanthamine had to be able to
 11 cross into the brain to release ACTH and cortisol.
 12 - - -
 13 A. (Continuing) The second thing is that the receptor
 14 type of two major receptors, the nicotinic and muscarinic
 15 receptors that galanthamine was acting upon was the nicotinic
 16 receptor because atropine was administered first. Atropine
 17 is a blocker in the blood and takes out the ACTH, the
 18 muscarinic receptors.
 19 If you get release of the ACTH and release of the
 20 cortisol, you have to be acting at the nicotinic receptors in
 21 the central nervous system.
 22 - - -
 23
 24
 25

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1
2 Q. And just so the record is clear, would a person of
3 ordinary skill in the art in 1986 understand from the
4 paragraph at Column 1, Line 11 to 21, therefore, that Dr.
5 Davis was saying that galanthamine was enhancing central
6 nicotinic cholinergic function?
7 A. Yes.
8 Q. Okay. Let me then turn to the second paragraph in
9 Column 1, which is from Lines 22 to 25.
10 Do you see there's a description of -- let me
11 try, Ilyuchenok and the appearance of --
12 MS. ULRICH: Your Honor, I'm sorry to interrupt,
13 but I have an objection to this.
14 Nothing that Dr. Raskin just testified about with
15 respect to the nicotinic receptors and what the art would
16 teach was disclosed in his expert report, so we object. This
17 is outside the scope and it's the first time that, frankly,
18 we're hearing this.
19 MR. SIPES: Your Honor, we disagree. There's an
20 extension section on enablement on the way in which a person
21 of ordinary skill in the art would understand what the patent
22 teaches.
23 THE COURT: Well, as I've always -- as I have
24 come to deal with expert reports and testimony at trial, I
25 will let it in. If an opposing party believes that it truly

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1 is outside the scope of both the report and the deposition
2 and that they were truly surprised, it will be brought up in
3 post-trial, and the party proposing the testimony is at risk,
4 obviously, for any retrial that might have to happen.
5 So you can certainly go forward, but I think that
6 my standard has been clearly explained.
7 MR. SIPES: Thank you, your Honor.
8 BY MR. SIPES:
9 Q. Let me ask you, what would a person of ordinary skill
10 in the art understand from the paragraph describing
11 Ilyuchenok about galanthamine?
12 A. Well, this, as -- this is animal data in rabbits in,
13 from which one can infer that peripherally administered into
14 the vein, intravenous galanthamine, crosses the blood/brain
15 barrier and affects brain waves.
16 Q. And let me then turn to the third paragraph.
17 There's -- the third paragraph, which is Column 1, Lines 26
18 to 28, is a discussion of Krauz.
19 What would a person of ordinary skill in the art
20 in 1986 understand from the discussion of Krauz?
21 A. That the -- that galanthamine, when, again, when
22 administered to -- in an animal model, in this case, to a
23 dog, increased short-term memory, which obviously is the
24 cardinal symptom of Alzheimer's disease.
25 Q. And let me turn to the next paragraph in Column 1,

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1 the brain. That is damaged in Alzheimer's disease. And this
2 model damages the site of origin of these pre-synaptic
3 acetylcholine neurons, which are indicated in the nucleus
4 basalis of Menert, and therefore, with damage to the
5 pre-synaptic cholinergic neurons in this nucleus, you get
6 an acetylcholine deficiency in the thinking parts of the
7 brain, in the hippocampus and the -- and the neocortex.

8 And this really does, if you will, at least in
9 part, mimic the cholinergic deficiency in Alzheimer's
10 disease. Either gets at the basic, the basic lesion in --
11 at cholinergic system in Alzheimer's disease.

12 Q. Now, which part of the central cholinergic system does
13 scopolamine block?

14 A. It blocks the post-synaptic system, the muscarinic
15 receptor in the thinking part. So it ignores the whole other
16 part that's damaged in Alzheimer's disease.

17 Q. And is the model that is set forth for Alzheimer's
18 disease in the patent, is that limited to the muscarinic
19 part?

20 A. No.

21 Q. What else does it include?

22 A. Well, it real really will affect all parts of -- all
23 receptors for acetylcholine in the brain, because you're
24 taking away acetylcholine, so all receptors will see less
25 acetylcholine and will be stimulated less.

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1 Q. Would it include the nicotinic receptor?

2 A. Yes.

3 Q. Would a person of ordinary skill in the art in 1986
4 recognize these differences between the model being proposed
5 for Alzheimer's disease in the patent and the scopolamine
6 model?

7 A. Yes.

8 Q. Would a person of ordinary skill in the art in 1986
9 recognize that the model for Alzheimer's disease set forth in
10 the patent includes the nicotinic as well as the muscarinic
11 function?

12 A. Yes.

13 Q. Let me draw your attention to the reference to numerous
14 behavioral deficits, including the inability to learn and
15 retain new information, characterizes this lesion. Does this
16 reference nicotinic and muscarinic function?

17 A. Yes.

18 Q. Would a person of ordinary skill in 1986 reading that
19 recognize that?

20 A. Yes.

21 Q. And how does that description differ from the earlier
22 scopolamine model?

23 A. Well, the scopolamine model is -- is just one-half,
24 if you will, of the -- of the cholinergic system, and it
25 is one that -- you know, doesn't mimic Alzheimer's disease,

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1 but does show you what happens when there's not enough
2 acetylcholine in the brain in terms of the functions of the
3 muscarinic side of the cholinergic system.

4 Q. And then the next sentence says, drugs that can
5 normalize these abnormalities would have a reasonable
6 expectation of efficacy in Alzheimer's disease.

7 Do you see that?

8 A. That is a reasonable inference.

9 Q. Now, we have gone over earlier the evidence about
10 galanthamine as presented in the patent.

11 Would any of that evidence bear on whether or not
12 galanthamine would be expected to succeed in this model to a
13 person of ordinary skill in the art in 1986?

14 A. Yes.

15 Q. Could you explain that?

16 A. The -- the earlier parts of the patent describe that
17 galanthamine gets in the brain, it's a cholinesterase
18 inhibitor.

19 So we know that it's going to increase the amount
20 of acetylcholine in the synapse that both types of receptors
21 see, but it -- it also -- the earlier part of the patent
22 would assure that the nicotinic part of the cholinergic
23 system would not be ignored by this drug, because this drug
24 has been demonstrated to affect the cholinergic system and
25 has to be at the nicotinic site when the muscarinics are

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1 taken out of the picture by administering atropine.

2 Q. So would a person of ordinary skill in the art in 1986
3 reading the patent believe that the assertion in the patent
4 that galanthamine is a treatment for Alzheimer's disease was
5 supported by the evidence presented for the effects of
6 galanthamine and the model for Alzheimer's disease
7 presented?

8 A. Yes.

9 Q. I believe you heard defendants' experts suggest that
10 Dr. Bonnie Davis' invention was just a guess. Did you hear,
11 I think it was Dr. Levy said, if the Court rejected his
12 obviousness testimony, then his testimony was that it was a
13 guess. Do you recall that?

14 A. Yes.

15 Q. Do you believe a person of ordinary skill in the art in
16 1986, reading the patent and its description of galanthamine
17 and its description of a model for Alzheimer's disease, would
18 view the invention as just a guess?

19 A. No.

20 Q. What -- how would they see it?

21 A. Well, I tell you how I saw it as a person in the art.
22 I certainly wouldn't have come up with this. I was impressed
23 that Dr. Davis did.

24 I think that the way it looks to me is that what
25 happens -- what happened here is what happens in science so

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1 many times. If you bring knowledge from one area, in this
2 case, endocrinology, as Dr. Bonnie Davis really brought
3 endocrinology expertise, to another area, in this case,
4 neuropsychiatry, and the two, you know, don't talk that much
5 on a daily basis, but here they were.

6 And so she brings insights from another area to
7 neurology neuropsychiatry and says, gee, you know, here's --
8 oh, the neuropsychiatrist teacher that -- there's this thing
9 called Alzheimer's disease and it is occurring in the brain
10 and it is marked by a cholinergic deficit, and she knows from
11 her endocrinology that, wow, there's this drug that has been
12 used in anesthesia that crosses into the brain and increases
13 acetylcholinergic activity. Not only does it do that, but it
14 seems to have a broad spectrum of action. Particularly it
15 has this nicotinic effect. Looks like a good -- a good go
16 for Alzheimer's disease.

17 Q. So would a person of ordinary skill in the art in 1986
18 view Dr. Bonnie Davis' invention as set forth in the patent
19 as scientifically grounded?

20 A. Yes.

21 Q. Okay. Let me then try to finish up by bringing up a
22 few things from yesterday.

23 You recall we talked about one of the old Eastern
24 European articles we're relying on, Pernov?

25 A. Yes.

1
2 BY MS. ULRICH:
3 Q. Do you see that, Doctor?
4 A. Yes, I do.
5 Q. Okay. I wish my voice was louder. It's not.
6 A. Your voice is fine.
7 Q. You can hear me?
8 A. Yes.
9 Q. Good. So this is your second expert report. Does this
10 look familiar?
11 A. Yes, it does.
12 Q. Okay. And is this the section where you opined on
13 enablement?
14 A. Yes.
15 Q. Okay. And it STATES, Dr. Domino and Dr. Levy asserted
16 that the '318 patent does not meet the enablement requirement
17 of patent law because quote it would not inform one of
18 ordinary skill in the art that galanthamine would be a
19 therapeutically effective treatment for Alzheimer's disease,
20 close quote.
21 Do you see that?
22 A. Yes.
23 Q. You say I disagree?
24 A. Yes.
25 Q. You go on to explain why you disagree?

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1 A. Yes.
2 Q. Do you see that?
3 A. Yes.
4 Q. This is what you said when you did your expert report:
5 The '318 patent states directly that galanthamine is a
6 therapeutically effective treatment for Alzheimer's disease.
7 By that you mean it claims a therapeutically effective
8 treatment for Alzheimer's disease?
9 A. Yes.
10 Q. That's just what the claim says?
11 A. Yes.
12 Q. You say, it outlines an approach for Alzheimer's
13 disease researchers to confirm the efficacy and tolerability
14 of the invention by providing the steps appropriate for
15 confirming Dr. Bonnie Davis' insight concerning
16 galanthamine -- most significantly, the manner of carrying
17 out animal testing to confirm the proposed efficacy.
18 Do you see that?
19 A. Yes, I do.
20 Q. And you made a point of saying, most significantly, it
21 was the animal model; is that right?
22 A. Yes.
23 Q. Okay. And nowhere in this paragraph do you indicate
24 that the prior art would have actually given a person of
25 skill in the art the expectation that this would work, do

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1 you?
2 MR. SIPES: Objection, your Honor. That's very
3 misleading.
4 THE WITNESS: It says it would be an effective
5 treatment for Alzheimer's disease.
6 BY MS. ULRICH:
7 Q. Based on the animal model. That's what you say here.
8 A. Yes.
9 Q. Okay.
10 A. Yes.
11 Q. All right. I want to talk about the Cozanitis article
12 that you reference in this patent. Go to the background art
13 section.
14 MS. ULRICH: Please put up PX-1.
15 BY MS. ULRICH:
16 Q. Dr. Raskin, this is the '318 patent; is that correct?
17 A. That's correct.
18 Q. Can you see that, Doctor?
19 A. I do.
20 Q. Okay. Now, as I understand your testimony, you say
21 that anybody, a person of skill in the art would have known
22 the Cozanitis' reference to atropine would necessarily
23 indicate that you were blocking the muscarinic receptors and
24 therefore this must be having a nicotinic effect?
25 A. That's a reasonable interpretation.

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1 to use galanthamine for peripheral conditions and not
2 central?
3 A. Peripheral.
4 Q. Peripheral?
5 A. Yes.
6 Q. Okay. And what about potency? Is it your opinion
7 that galanthamine is not as potent as physostigmine?
8 A. That's my opinion.
9 Q. Okay. And those three things combined would have led
10 somebody away from choosing galanthamine. Is that your
11 testimony?
12 A. Yes. That's -- that's what the field was feeling at
13 the time.
14 Q. Okay. Because a person of skill in the art wouldn't
15 recognize that a drug that was less potent, of equal
16 duration of action as physostigmine and had been used
17 peripherally would be expected to work in Alzheimer's
18 disease; correct?
19 A. Would be expected to work?
20 Q. Would not be expected to work.
21 A. Well, it's certainly less likely than physostigmine
22 and physostigmine didn't seem to be working, so why choose
23 galanthamine.
24 Q. Right. You claim that physostigmine wasn't working as
25 of 1986; right?

1 Q. If you would like --
 2 A. Yes.
 3 Q. -- to have it in front of you.
 4 A. Yes.
 5 Q. Column 1, the first page of text.
 6 You'll recall that Ms. Ulrich asked you a
 7 number of questions about each of the pieces of prior
 8 art that is described in the patent, taken one by one. Do
 9 you recall that?
 10 A. Yes.
 11 Q. And I think one of the things she pointed out, do
 12 you recall, was that, for example, atropine, depending
 13 on how it's administered, may have different effects;
 14 correct?
 15 A. Yes.
 16 Q. And that somebody reading Cozanitis alone might
 17 not recognize the nicotinic effect of galanthamine. Do
 18 you recall that?
 19 A. That was the implication.
 20 Q. And I believe, in fact, you'll recall the testimony
 21 from yesterday I think from Dr. Bonnie Davis, that, in
 22 fact, Cozanitis himself thought it might be a stress
 23 response. Do you recall that?
 24 A. Yes.
 25 Q. But now I want to ask you, take the description of

1 background art, would that be affected by the presentation
 2 of the art all assembled together like this along with a
 3 model for Alzheimer's disease that was the selective
 4 lesion model?
 5 A. Yes. I mean, this would -- this would do it.
 6 Q. Let me ask you, Ms. Ulrich asked you a couple of
 7 questions about all of the other failed attempts that
 8 you testified to other than the cholinergic attempt, the
 9 ones to the left and all the ones to the right.
 10 A. Mm-hmm.
 11 Q. She asked whether or not those were the same, I
 12 guess, category of attempts as in the '318 patent. Do you
 13 recall that?
 14 A. Yes.
 15 Q. Let me ask you this: Were all of those attempts to
 16 find symptomatic treatments for Alzheimer's disease?
 17 A. Yes.
 18 Q. Now, she also suggested that they may have had other
 19 logic. But let me ask you: Was there an attempt to use
 20 piracetam in combination with a precursor to address the
 21 cholinergic deficit hypothesis?
 22 A. Yes.
 23 Q. Would that use of piracetam be following the same
 24 logic -- well, would that attempt be another attempt to
 25 address the cholinergic deficit hypothesis?

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1 the Cozanitis articles in the patent in the context of
 2 the patent, in the context of all the other art assembled
 3 in the patent and the description of the animal model in
 4 the patent.
 5 What would a person of ordinary skill in the
 6 art understand the inventor to be saying about
 7 galanthamine as described in the Cozanitis papers when
 8 it's assembled this way?
 9 A. Well, it -- it's saying that in a reasonable model
 10 for Alzheimer's disease, cholinergic deficit, galanthamine
 11 would account for the nicotinic side of the cholinergic
 12 system.
 13 Q. And would a person of ordinary skill in the art,
 14 seeing a model described that was a cholinergic deficiency
 15 model for Alzheimer's in a patent that also cited
 16 Cozanitis, would they be -- would they be inclined -- how
 17 would they read the Cozanitis results in light of its
 18 presentation of patent that sets forth the cholinergic
 19 model?
 20 A. It suggests that it's a nicotinic receptor stimulating
 21 compound.
 22 Q. And let me ask you, generally, would the reading, a
 23 person of ordinary skill in the art, a teaching that a
 24 person of ordinary skill in the art would take away from
 25 the evidence about galanthamine in the papers under

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1 Q. Did you -- did you do that with an expectation --
2 did you do that with a hope for success?
3 A. Yes.
4 Q. All right.
5 Q. You recall Ms. Ulrich asked you a few questions
6 about Dr. Domino's 1988 paper?
7 A. Yes.
8 Q. Now, do you recall that Dr. Domino testified that
9 he was actually asked to do the talk in the spring of
10 '88 that led to the paper later that year?
11 A. Yes.
12 Q. By a Doctor Ezio Giacobini?
13 A. Yes.
14 Q. Are you familiar with Dr. Giacobini?
15 A. I am.
16 Q. Is he an expert in cholinesterase inhibitors?
17 A. Yes.
18 Q. Does he keep up with the literature on cholinesterase
19 inhibitors?
20 A. Yes.
21 Q. In your experience with him, does he intend to be
22 very knowledgeable about cholinesterase inhibitors?
23 A. Extremely.
24 Q. Now, in 1988, is it correct that both the '318
25 patent and Dr. Coyle's preliminary results on

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1 galanthamine in the lesion model for Alzheimer's had been
2 published?
3 A. Yes.
4 Q. Now, I think you asked repeatedly for the 1985 paper
5 in which the physostigmine results in their full entirety
6 were published.
7 A. Yes.
8 Q. Do you recall that?
9 A. That's correct.
10 Q. If you could look behind Tab 30...
11 A. Yes, I have it.
12 Q. You'll see this is Plaintiffs' Exhibit 698, a
13 document entitled Clinical Studies of the Cholinergic
14 Deficit in Alzheimer's Disease.
15 Do you see that?
16 A. I do.
17 Q. Is this the paper that you were referring to?
18 A. It is.
19 Q. And it's published in the Journal of the American
20 Geriatric Society in 1985?
21 A. Yes.
22 MR. SIPES: I move Plaintiffs' Exhibit 698
23 into evidence.
24 MR. GRACEY: No objection.
25 THE COURT: Thank you.

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EXHIBIT 8

REDACTED

EXHIBIT 9

1 plaintiffs have produced evidence that indicates how
2 everyone was and, frankly, still is, to some extent,
3 struggling to unravel the mysteries of Alzheimer's.

4 Defendants have produced evidence that the
5 scientific community was focused on the cholinergic
6 deficit theory and that galanthamine was an obvious
7 drug of choice in that context.

8 On the issue of enablement, however,
9 plaintiffs have produced evidence that the handful of
10 scientific papers cited in the '318 patent is a clear
11 explanation of the inventive process and that titration
12 was a well-known methodology of -- in terms of
13 administering the drug. And there is other evidence in
14 the record, however, that Alzheimer's was so little
15 understood in 1986, that the '318 patent explained
16 little, if anything, to the scientific community, and,
17 further, because everyone was looking for the kind of
18 miracle drug that dopamine was, that titration would
19 be very tricky with galanthamine because there are no
20 immediate effects, just a slowing of an inevitable
21 decline.

22 So the bottom line is you've left me with a
23 complicated record, albeit a most interesting one, and
24 I look forward to seeing how you all sort out the record
25 in your post-trial briefing.

EXHIBIT 10

REDACTED

EXHIBIT 11

REDACTED

EXHIBIT 12

REDACTED

CERTIFICATE OF SERVICE

I hereby certify that on the 30th day of August, 2007, the attached **REDACTED PUBLIC VERSION OF APPENDIX I: TRIAL TRANSCRIPT EXCERPTS** was served upon the below-named counsel of record at the address and in the manner indicated:

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